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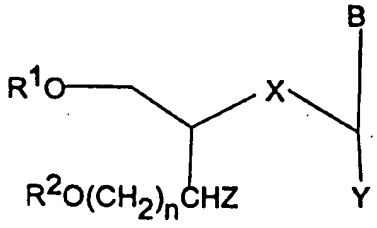

(I)

(57) Abstract

Mixed esters of antiviral nucleosides such as compounds of Formula (I), where B is natural or unnatural nucleotide base, X is O or CH_2, Y and Z are each H, or together form a bond, or Y is methylene or -CH(OH)- and Z is a bond thereto; n is 0 or 1; one of R_1 and R_2 is the acyl residue of an aliphatic amino acid and the other is $-C(=O)C_5-C_{21}$ saturated or monounsaturated alkyl; and pharmaceutically acceptable salts thereof have advantageous pharmacokinetic and other properties.

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Nucleosides

Technical Field

This invention relates to the field of nucleosides and nucleoside analogues. The invention provides novel compounds, pharmaceutical compositions comprising these compounds, methods for their manufacture and methods for the treatment or prophylaxis of cancers and viral infections employing these compounds.

Background to the invention

The practical utility of many acyclic nucleosides is limited by their relatively modest pharmacokinetics. A number of prodrug approaches have been explored in an effort to improve the bioavailability of acyclic nucleosides in general. One of these approaches involves the preparation of ester derivatives, particularly aliphatic esters, of one or more of the hydroxy groups on the acyclic side chain.

Harnden, et al., J. Med. Chem. 32, 1738 (1989) investigated a number of short chain aliphatic esters of the acyclic nucleoside 9-[4-hydroxy-(3-hydroxymethyl)butyl] guanine, otherwise known as penciclovir, and its 6-deoxy analog. Famciclovir, a marketed antiviral agent, is the diacetyl derivative of 6-deoxy penciclovir.

Benjamin, et al., Pharm. Res. 4 No. 2, 120 (1987) discloses short chain aliphatic esters of 9-[(1,3-dihydroxy-2-propoxy)-methyl]guanine, otherwise known as ganciclovir. The dipropionate ester is disclosed to be the preferred ester.

Lake-Bakaar, et al., discloses in Antimicrob. Agents Chemother. 33 No. 1, 110-112 (1989) diacetate and dipropionate derivatives of the acyclic nucleoside H2G and monoacetate and diacetate derivatives of 6-deoxy H2G. The diacetate and dipropionate derivatives of H2G are reported to result in only modest improvements in bioavailability relative to H2G.

International patent application WO94/24134, published October 27, 1994, discloses aliphatic ester prodrugs of the 6-deoxy N-7 analog of ganciclovir, including the di-pivaloyl, di-valeroyl, mono-valeroyl, mono-oleoyl and mono-stearoyl esters.

International patent application WO93/07163, published April 15, 1993 and International patent application WO94/22887, published October 13, 1994, both disclose mono-ester derivatives of nucleoside analogs derived from mono-unsaturated C18 or C20 fatty acids, including araT, araA and ribavirin. U.S. Patent No. 5,216,142, issued June 1, 1993, also discloses long chain fatty acid mono-ester derivatives of nucleoside analogs.The preparation and esterification of ribavirin is described in WO 94/22887 and US 3984396.

Rubas et al Int J cancer 37 No 1 149-154 (1986) describe the N^4 and O^4 oleyl and palmityl esters of araC and conclude that the N^4 oleyl derivative was the most effective. Schott et al in Biol Chem Hoppe Seyler 368, No 7, 773 (1987) report that N^4-acyl araC exert in vivo a 2 to 8 fold antitumour activity compared to araC. International patent application no WO 92 01456 describes 6-alkoxy araG derivatives with enhanced bioavailability. However modifed bases have a number of shortcomings. One of these potential problems is especially in nucleosides where the 3' and 5' hydroxy groups of the sugar moiety are accesible for phosphorylating and polymerase enzymes, such modified bases are occasionally incorporated into DNA, leading to DNA damage and in the worst case carcinogenicity or inheritable mutations. A further shortcoming is that if the base is hydrolysed from the saccharide, the modified base thus released is often considerably more toxic than the corresponding natural base.

A second approach to providing prodrugs of acyclic nucleosides involves the preparation of amino acid esters of one or more of the hydroxy groups on the acyclic side chain. European patent EP 99 493 discloses generally amino acid esters of

acyclovir and European patent application EP 308 065, published March 22, 1989, discloses the valine and isoleucine esters of acyclovir.

European patent application EP 375 329, published June 27, 1990, discloses amino acid ester derivatives of ganciclovir, including the di-valine, di-isoleucine, di-glycine and di-alanine ester derivatives. International patent application WO95/09855, published April 13, 1995, discloses amino acid ester derivatives of penciclovir, including the mono-valine and di-valine ester derivatives.

DE 19526163, published February 1, 1996 and U.S. Patent no. 5,543,414 issued August 6, 1996 , disclose achiral amino acid esters of ganciclovir.

European patent application EP 694 547, published January 31, 1996, discloses the mono-L-valine ester of ganciclovir and its preparation from di-valyl-ganciclovir. International patent applications WO 97/27194-27197 describe additional preparations of monovalyl ganciclovir.

European patent application EP 654 473, published May 24, 1995, discloses various bis amino acid ester derivatives of 9-[1',2'-bishydroxymethyl)-cyclopropan-1'yl] methylguanine.

International patent application WO95/22330, published August 24, 1995, discloses aliphatic esters, amino acid esters and mixed acetate/valinate esters of the acyclic nucleoside 9-[3,3-dihydroxymethyl-4-hydroxy-but-1-yl]guanine. This reference discloses that bioavailability is reduced when one of the valine esters of the trivaline ester derivative is replaced with an acetate ester.

International patent application WO 89 03837 has claims encompassing nucleoside 2', 3' and/or 5' amino/fatty acid esters although there is no specific disclosure of nucleosides with mixed esters.

Dae-Kee Lim et al in Bioorg. & Med. Chem. Lett. Vol 6 No 15 pp 1849-1854, 1996 describe a series of penciclovir derivatives with valine/isoleucine in conjunction with acetyl, propionyl or butyryl esters. In that study the best pharmacokinetic performance of a mixed ester was with acetyl, that is the shortest possible alkyl ester component. Performance markedly tailed off by lengthening the alkyl chain with just one or two methylene units.

Starret et al in J.Med.Chem. (1994) 37 No 12 1857-1884 describe the preparation of a series of phosphonate prodrugs of the acyclic antiviral 9-[2-(phosphonomethoxy)-ethyl]adenine including a mixed alkyl (acyloxy)alkyl ester which was absorbed but underwent incomplete hydrolysis to the monoethyl ester.

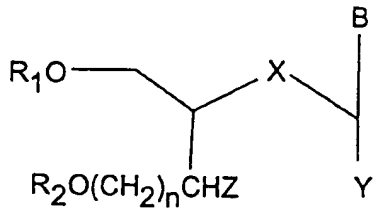
The applicant's co-pending international patent applications WO 97/30051 and 30052, published on 21st August 1997 (that is after the priority date of the present application) discloses fatty acid/amino acid esters of the acyclic nucleoside 9-[4-hydroxy-(2-hydroxymethyl)butyl]guanine and its 6-deoxy derivative.

Brief Description of the Invention

We have now discovered that acylating antiviral nucleosides bearing at least two free hydroxy groups with a combination of specified amino and particular fatty acid esters produces nucleosides with good bioavailabilities and other beneficial properties.

The combined esters of the present invention are generally applicable to nucleosides having at least two free hydroxy groups, preferably in the saccharidic or acyclic moiety of the nucleoside, with the proviso that the nucleoside is not 9-[4-hydroxy-(2-hydroxymethyl)butyl]guanine or its 6-deoxy derivative.

However, a particularly preferred group of compounds within the scope of the invention has the formula I



I

where B is a natural or unnatural nucleotide basc,

X is O or -CH_2-

Y and Z are each H or Y is methylene or -CH(OH)- and Z is a bond thereto, or Y and Z together are a bond;

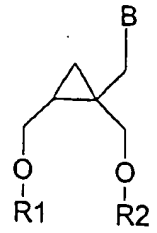
n is 0 or 1;

onc of R_1 and R_2 is the acyl residue of an aliphatic amino acid and the other is -C(=O)C_5-C_{21} saturated or monounsaturated optionally substituted alkyl;

and pharmaceutically acceptable salts thereof.

In compounds wherein Y is -CH(OH)-, one of R_1 or R_2 may alternatively or additionally be acylated to the 2'-hydroxy, but it is preferred that R_1 and R_2 dcpcnd from the 3' and 5' positions of the nucleoside or analogue.

An alternative group of compounds within the scope of the invention has the formula Ia:

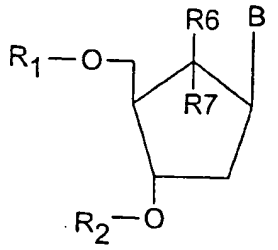


Ia

where B, R_1 and R_2 are as defined above. Reprcsentative examples within this group includc: 9-[1'-valyloxymethyl-2'-dodecanoyloxymethyl)-cyclopropan-1'yl] mcthylguaninc, 9-[1'-valyloxymethyl-2'-tetradecanoyloxymethyl)-cyclopropan-1'yl] methylguanine, 9-[1'-valyloxymethyl-2'-hexadecanoyloxymethyl)-cyclopropan-1'yl] methylguanine, 9-[1'-valyloxymethyl-2'-octadecanoyloxymethyl)-cyclopropan-1'yl] methylguanine, 9-[1'-

valyloxymethyl-2'-eicosanoyloxymethyl)-cyclopropan-1'yl] methylguanine, 9-[1'-valyloxymethyl-2'-docosanoyloxymethyl)-cyclopropan-1'yl] methylguanine, 9-[1'-dodecanoyloxymethyl-2'-valyloxymethyl)-cyclopropan-1'yl] methylguanine, 9-[1'-tetradecanoyloxymethyl-2'-valyloxymethyl)-cyclopropan-1'yl] methylguanine, 9-[1'-hexadecanoyloxymethyl-2'-valyloxymethyl)-cyclopropan-1'yl] methylguanine, 9-[1'-octadecanoyloxymethyl-2'-valyloxymethyl)-cyclopropan-1'yl] methylguanine, 9-[1'-eicosanoyloxymethyl-2'-valyloxymethyl)-cyclopropan-1'yl] methylguanine, and the corresponding isoleucyl analogues.

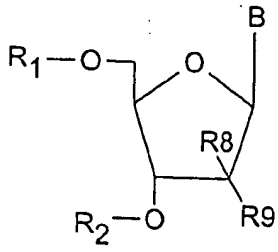
An alternative group of compounds within the scope of the invention has the formula Ib:



Ib

where B, R_1 and R_2 are as defined above and R6 is fluoro and R7 is hydrogen or R6 and R7 are both fluoro or R6 and R7 together define an exo-methenyl group. The preferred base is guanine in this alternative.

A further group of nucleosides within the scope of the invention has the formula Ic



Ic

where B, R_1 and R_2 are as defined above, R8 and R9 are fluoro (or one of them is fluoro and the other is hydrogen) or R8 and R9 together define exomethenyl or

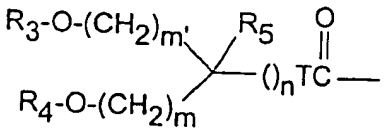
exomethenyl mono or di-subsituted with fluoro. These nucleosides have anticancer activity.

The invention is also applicable to phosphonylated antivirals such as (s)-1-3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (cidofovir, HPMPC), as described in US 5 142 051. In this case one of the R^1 and R^2 may be esterified to an hydroxy group on the phosphonyl moiety, preferably via an intermediate -CH(R^3)-O- group where R^3 may be hydrogen, methyl, isopropyl or the like, whereas the other of R^1 and R^2 may be esterified to the hydroxy group on the 3-hydroxy group. Alternatively both R^1 and R^2 may be esterified to a respective hydroxy group on the phosphonyl moiety preferably via respective intermediate -CH(R^3)-O-groups. This latter arrangement will also be applicable to phosphonylated nucleosides such as 9-[2-(phosphono-methoxy)ethyl]adenine (adefovir, PMEA) as described in US 5 476 938. If a 3-hydroxy group is present, this may optionally be acylated with an additional R^1 or R^2. When applied to such phosphonylated nucleosides, the saturated or monounsaturated alkyl component may have from 5 to 21 carbon atoms, viz a fatty acid ester with 6 to 22 carbon atoms including the carbonyl.

Preferred compounds of the aspect of the invention described in the paragraph immediately above include 9-[2-(phosphonomethoxy)ethyl]adenine, monovalyloxymethyl, monohexanoyloxymethyl ester; 9-[2-(phosphonomethoxy)ethyl]adenine, monovalyloxymethyl, monooctanoyloxymethyl ester; 9-[2-(phosphonomethoxy)ethyl]adenine, monovalyloxymethyl, monodecanoyloxymethyl ester; 9-[2-(phosphonomethoxy)ethyl]adenine, monovalyloxymethyl, monododecanoyloxymethyl ester; 9-[2-(phosphonomethoxy)ethyl]adenine, monovalyloxymethyl, monotetradecanoyloxymethyl ester; 9-[2-(phosphonomethoxy)ethyl]adenine, monovalyloxymethyl, monohexadecanoyloxymethyl ester; 9-[2-(phosphonomethoxy)ethyl]adenine, monovalyloxymethyl, monooctadecanoyloxymethyl ester; 9-[2-(phosphonomethoxy)ethyl]adenine, monovalyloxymethyl, monoeicosanoyloxymethyl ester; 9-[2-

(phosphonomethoxy)ethyl]adenine, monovalyloxymethyl, monodocosanoyloxymethyl ester; and the corresponding isoleucyl analogues of each of the above.

A further application of the combined fatty acid and amino acid esters of the invention is to apply both esters to a common linking group, which linking group is itself esterified to an hydroxyl function of a dihydroxylated nucleoside or nucleoside analogue such as the hydroxyl function marked R^1 or R^2 in Formula I, Ia, Ib or Ic above. The other of R^1 or R^2 will generally be hydrogen, but may also bear an additional linker structure as defined herein or be acylated as for R^1 or R^2. The common linking group may be configured as in formula II below:



II

where

one of R_3 and R_4 is the acyl residue of an aliphatic amino acid and the other is $-C(=O)C_5-C_{21}$ saturated or monounsaturated, optionally substituted alkyl;
R_5 is H or C_1-C_3 alkyl;
T is a bond, O or NH;
m and m' are independently 0, 1 or 2 and n is 0-5,

Preferably m is 1 and/or n is 0, 1 or 2 and/or T is a bond or -O-. Especially when T is a bond it is preferred if n is 0 or 1. Conveniently, n and m are not both 0. R_5 is preferably H. The moiety denoted $()_n$ preferably comprises an alkane chain but can bear an unsaturated bond.

This aspect of the invention contemplates the application of the linking group, such as those of formula II, to nucleosides having at least two hydroxy groups, but outside the scope of formula I, Ia, Ib or Ic, for instance, 9-[3,3-dihydroxymethyl-4-

hydroxy-but-1-yl]guanine as described in WO 95/22330 and 9-[4-hydroxy-(2-hydroxymethyl)butyl]guanine as described in EP 343 133.

The invention also provides pharmaceutical compositions comprising the compounds of the invention, such as those of Formula I, Ia, Ib, Ic or I/II (that is a structure of formula I, Ia, Ib or Ic in conjunction with a structure of the formula II) or mixed esters of phosphonylated antivirals, and their pharmaceutically acceptable salts in conjunction with a pharmaceutically acceptable carrier or diluent. Further aspects of the invention provide the compounds of the invention and their pharmaceutically acceptable salts for use in therapy and the use of these compounds and salts in the preparation of a medicament for the treatment or prophylaxis of cancers and viral infection in humans or animals.

The invention further provides the use of a combination of an optionally substituted, saturated or monounsaturated fatty acid ester having 6 to 22 carbon atoms (that is an $-C(=O)C_5-C_{21}$ saturated or monounsaturated, optionally substituted alkyl moeity) and an aliphatic amino acid ester for modifying the pharmacokinetics of nucleoside analogues having at least two hydroxy groups on the saccharide or acyclic moiety (with the exclusion of 9-[4-hydroxy-(2-hydroxymethyl)butyl]guanine and its 6-deoxy derivative) and/or (if present) the phosphonate moiety. A still further aspect of the invention provides the use of a linker group having esterified thereon an optionally substituted, saturated or monounsaturated fatty acid ester having 6 to 22 carbon atoms (that is an $-C(=O)C_5-C_{21}$ saturated or monounsaturated, optionally substituted alkyl moeity) and an aliphatic amino acid ester for modifying the pharmacokinetics of nucleoside analogues having at least two hydroxy groups on the saccharide or acyclic moiety.

The compounds of the invention, particularly guanine derivatives where X is O or CH_2 and Y and Z are H are potent antivirals, especially against herpes infections, such as those caused by Varicella zoster virus, Herpes simplex virus types 1 & 2, Epstein-Barr virus, Herpes type 6 (HHV-6) and type 8 (HHV-8).

The compounds of the invention, especially cytosine or guanine derivatives where X is oxygen, n is 1 and Y and Z define a ring are also active against certain retroviral infections, notably SIV, HIV-1 and HIV-2, and Hepatitis B virus.

The compounds of the invention, especially cytosine, guanosine or 6-methoxyguanosine derivatives wherein X is oxygen, n is 0 and Y and Z define an arabinose ring are potent anticancer compounds.

The compounds of the invention, especially derivatives comprising a 1,2,4-triazole-3-carboxamide base, where X is O, Y is -CH(OH)-, Z is a bond thereto and n is 0 (ribavirin) are expected to be active against hepatitis C virus (HCV). Compounds comprising a substituted benzimidazole base, where X is O, Y is -CH(OH)-, Z is a bond thereto and n is 0 (for instance Glaxo Wellcome's 1263W94 where the base is 2-isopropylamin-5,6-dichloro-benzimidazol-3-yl) are expected to be active against CMV. Compounds comprising an adenine base, where X is O, Y is -CH(OH)-, Z is a bond thereto and n is 0 (vidarabine) are expected to be active against HSV encephalitis. Compounds comprising a 2-chloroadenine base with a 2'-deoxyribose sugar are expected to ghave anticancer activity.

Accordingly a further aspect of the invention provides a method for the prophylaxis or treatment of cancers or viral infections in humans or animals comprising the administration of an effective amount of a compound of the invention, such as those of Formula I, Ia, I/II or mixed esters of phosphonylated antivirals or its pharmaceutically acceptable salt to the human or animal.

The nucleoside derivatives of the invention are particularly useful for guanine nucleoside and analogues which tend to have poorer uptake than pyrimidine nucleosides. Accordingly B is preferably guanine or a guanine derivative. Guanine bases are advantageously modified at the 6 position to define an even more readily soluble 6-deoxy derivative which can be oxidised in vivo (e.g. by xanthine

oxidase) to the guanine form. Alternatively guanine bases can be present in the 6-alkoxy form.

Preferred bases when Y and Z are hydrogen or together form a bond include adenine and especially guanine. Other preferred bases include cytosine, especially when X is oxygen, n is 1 and Y and Z define a ring or n is 0 and Y is -C(OH)-..

Compounds wherein Y is -C(OH)- may define lyxofuranosyl or xylofuranosyl derivatives, but more preferably define arabinose or ribose derivatives.

Preferably the amino acid ester of group R_1 or R_3 is derived from an L-amino acid, such as leucine, alanine and especially L-valine or L-isolcucinc. The amino acid ester R_1 is preferably located on the 5' position of thc nucleoside.

The favoured fatty acid esters for R_2 and R_4 have the formula $-C(=O)C_{11}-C_{21}$ and preferably have an even number of carbon atoms, in particular, lauryl (C_{12}), myristoyl (C_{14}), palmitoyl (C_{16}), stearoyl (C_{18}), eicosanoyl (C_{20}) or behenoyl (C_{22}). Further useful R_2 groups include esters of myristoleic, myristelaidic, palmitoleic, palmitelaidic, n6-octadecenoic, oleic, elaidic, gandoic, erucic or brassidic acids. The fatty acid may optionally be substituted with up to five substituents independently sclected from the group consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkanoyl amino, halo, cyano, azido, oxo, mercapto or nitro, and the like. It is preferred if the fatty acid ester is unsubstituted.

Preferred compounds include:

9-[4-(L-isoleucyloxy)-3-(dodecanoyloxymethyl)butyl]guanine,

9-[4-(L-isoleucyloxy)-3-(tetradecanoyloxymethyl)butyl]guanine,

9-[4-(L-isoleucyloxy)-3-(hexadecanoyloxymethyl)butyl]guanine,

9-[4-(L-isoleucyloxy)-3-(octadecanoyloxymethyl)butyl]guanine,

9-[3-(eicosanoyloxymethyl)-4-(L-isoleucyloxy)butyl]guanine,

9-[3-(docosenoyloxymethyl)-4-(L-isoleucyloxy)butyl]guanine,

2-amino-9-[4-(L-isoleucyloxy)-3-(dodecanoyloxymethyl)butyl]purine,
2-amino-9-[4-(L-isoleucyloxy)-3-(tetradecanoyloxymethyl)butyl]purine,
2-amino-9-[4-(L-isoleucyloxy)-3-(hexadccanoyloxymethyl)butyl]purine,
2-amino-9-[4-(L-isoleucyloxy)-3-(octadecanoyloxymethyl)butyl]purine,
2-amino-9-[4-(L-isoleucyloxy)-3-(eicosanoyloxymethyl)butyl]purine,
2-amino-9-[3-(eicosanoyloxymethyl)-4-(L-isoleucyloxy)butyl]purine,
2-amino-9-[3-(docosanoyloxymethyl)-4-(L-isoleucyloxy)butyl]purine,
9-[3-(L-isoleucyloxy)-4-(dodecanoyloxymethyl)butyl]guanine,
9-[3-(L-isoleucyloxy)-4-(tetradecanoyloxymethyl)butyl]guanine,
9-[3-(L-isoleucyloxy)-4-(hexadecanoyloxymethyl)butyl]guanine,
9-[3-(L-isoleucyloxy)-4-(octadccanoyloxymethyl)butyl]guanine,
9-[4-(eicosanoyloxymethyl)-3-(L-isoleucyloxy)butyl]guanine,
9-[3-(docosanoyloxymethyl)-3-(L-isoleucyloxy)butyl]guanine,
2-amino-9-[3-(L-isoleucyloxy)-4-(dodecanoyloxymethyl)butyl]purine,
2-amino-9-[3-(L-isoleucyloxy)-4-(tetradecanoyloxymethyl)butyl]purine,
2-amino-9-[3-(L-isoleucyloxy)-4-(hexadecanoyloxymethyl)butyl]purine,
2-amino-9-[3-(L-isoleucyloxy)-4-(octadecanoyloxymethyl)butyl]purine,
2-amino-9-[3-(L-isoleucyloxy)-4-(eicosanoyloxymethyl)butyl]purine,
2-amino-9-[4-(eicosanoyloxymethyl)-3-(L-isoleucyloxy)butyl]purine,
2-amino-9-[4-(docosanoyloxymethyl)-3-(L-isoleucyloxy)butyl]purine,
and their pharmaceutically accepable salts.

Further preferred compounds include:
9-[3-(dodecanoyloxymethyl)-4-(L-valyloxy)butyl]guanine,
9-[3-(tetradecanoyloxymethyl-4-(L-valyloxy)butyl]guanine,
9-[3-hexadecanoyloxymethyl)-4-(L-valyloxy)butyl]guanine,
9-[3-(octadecanoyloxymethyl)-4-(L-valyloxy)butyl]guanine,
9-[3-(eicosanoyloxymethyl)-4-(L-valyloxy)butyl]guanine,
9-[3-(eicosanoyloxymethyl)-4-(L-valyloxy)butyl]guanine,
9-[3-(docosanoyloxymethyl)-4-(L-valyloxy)butyl]guanine,
2-amino-9-[3-(dodecanoyloxymethyl)-4-(L-valyloxy)butyl]purine,

2-amino-9-[3-(tetradecanoyloxymethyl)-4-(L-valyloxy)butyl]purine,
2-amino-9-[2-(hexadecanoyloxymethyl)-4-(L-valyloxy)butyl]purine,
2-amino-9-[3-(octadecanoyloxymethyl)-4-(L-valyloxy)-butyl]purine,
2-amino-9-[2-(eicosanoyloxymethyl)-4-(L-valyloxy)butyl]purine,
2-amino-9-[3-(docosanoyloxymethyl)-4-(L-valyloxy)butyl]purine
9-[4-(dodecanoyloxymethyl)-3-(L-valyloxy)butyl]guanine,
9-[4-(tetradecanoyloxymethyl-3-(L-valyloxy)butyl]guanine,
9-[4-hexadecanoyloxymethyl)-3-(L-valyloxy)butyl]guanine,
9-[4-(octadecanoyloxymethyl)-3-(L-valyloxy)butyl]guanine,
9-[4-(eicosanoyloxymethyl)-3-(L-valyloxy)butyl]guanine,
9-[4-(docosanoyloxymethyl)-3-(L-valyloxy)butyl]guanine,
2-amino-9-[4-(dodecanoyloxymethyl)-3-(L-valyloxy)butyl]purine,
2-amino-9-[4-(tetradecanoyloxymethyl)-3-(L-valyloxy)butyl]purine,
2-amino-9-[4-(hexadecanoyloxymethyl)-3-(L-valyloxy)butyl]purine,
2-amino-9-[4-(octadecanoyloxymethyl)-3-(L-valyloxy)-butyl]purine,
2-amino-9-[4-(eicosanoyloxymethyl)-3-(L-valyloxy)butyl]purine,
2-amino-9-[4-(docosanoyloxymethyl)-3-(L-valyloxy)butyl]purine,
and their pharmaceutically acceptable salts.

Preferred compounds include
2',3'-dideoxy, 3'-C-L-isoleucyloxymethyl-5'-dodecanoylcytosine
2',3'-dideoxy, 3'-C-L-isoleucyloxymethyl-5'-tetradecanoylcytosine
2',3'-dideoxy, 3'-C-L-isoleucyloxymethyl-5'-hexadecanoylcytosine
2',3'-dideoxy, 3'-C-L-isoleucyloxymethyl-5'-octadecanoylcytosine
2',3'-dideoxy, 3'-C-L-isoleucyloxymethyl-5'-eicosanoylcytosine
2',3'-dideoxy, 3'-C-L-isoleucyloxymethyl-5'-docosanoylcytosine
2',3'-dideoxy, 3'-C-(L-isoleucyloxymethyl-5'-dodecanoylcytosine
2',3'-dideoxy, 3'-C-L-isoleucyloxymethyl-5'-(9-tetradecanoyl)cytosine
2',3'-dideoxy, 3'-C-L-isoleucyloxymethyl-5'-(9-hexadecenoyl)cytosine
2',3'-dideoxy, 3'-C-L-isoleucyloxymethyl-5'-(9-octadecenoyl)cytosine
2',3'-dideoxy, 3'-C-L-isoleucyloxymethyl-5'-(11-eicosenoyl)cytosine

2',3'-didcoxy, 3'-C-L-isoleucyloxymethyl-5'-(11-docosenoyl)cytosine

2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-dodecanoylcytosine
2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-tetradecanoylcytosine
2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-hexadecanoylcytosine
2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-octadecanoylcytosine
2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-eicosanoylcytosine
2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-docosanoylcytosine
2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-(9-dodecenoyl)cytosine
2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-(9-tetradecenoyl)cytosine
2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-(9-hexadecenoyl)cytosine
2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-(9-octadecenoyl)cytosine
2',3'-didcoxy, 3'-C-L-valyloxymethyl-5'-(11-eicosenoyl)cytosine
2',3'-dideoxy, 3'-C-L-valyloxymethyl-5'-(11-docosenoylcytosine

2',3'-dideoxy, 3'-C-dodecanoyloxymethyl-5'-L-isoleucylcytosine
2',3'-dideoxy, 3'-C-tetradecanoyloxymethyl-5'-L-isoleucylcytosine
2',3'-dideoxy, 3'-C-hexadecanoyloxymethyl-5'-L-isoleucylcytosine
2',3'-dideoxy, 3'-C-octadecanoyloxymethyl-5'-L-isoleucylcytosine
2',3'-dideoxy, 3'-C-eicosanoyloxymethyl-5'-L-isoleucylcytosine
2',3'-dideoxy, 3'-C-docosanoyloxymethyl-5'-L-isoleucylcytosine
2',3'-dideoxy, 3'-C-(L-valyloxymethyl)-5'-dodecanoylcytosine
2',3'-dideoxy, 3'-C-(L-valyloxymethyl)-5'-tetradccanoylcytosine
2',3'-dideoxy, 3'-C-(L-valyloxymethyl)-5'-hcxadecanoylcytosine
2',3'-dideoxy, 3'-C-(L-valyloxymethyl)-5'-octadecanoylcytosine
2',3'-dideoxy, 3'-C-(L-valyloxymethyl)-5'-eicosanoylcytosine
2',3'-dideoxy, 3'-C-(L-valyloxymethyl)-5'-docosanoylcytosine
2',3'-dideoxy, 3'-C-dodecanoyloxymethyl-5'-L-valylcytosine
2',3'-dideoxy, 3'-C-tetradecanoyloxymethyl-5'-L-valylcytosine
2',3'-dideoxy, 3'-C-hexadecanoyloxymethyl-5'-L-valylcytosine
2',3'-dideoxy, 3'-C-octadecanoyloxymethyl-5'-L-valylcytosine

2',3'-dideoxy, 3'-C-eicosanoyloxymethyl-5'-L-valylcytosine
2',3'-dideoxy, 3'-C-docosanoyloxymethyl-5'-L-valylcytosine
and their pharmaceutically acceptable salts.

Further preferred compounds include
1-(3'-O-dodecanoyl-5'-O-valyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-tetradecanoyl-5'-O-valyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-hexadecanoyl-5'-O-valyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-stearoyl-5'-O-valyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-eicosanoyl-5'-O-valyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-docosanoyl-5'-O-valyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-dodecanoyl-5'-O-isoleucyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-tetradecanoyl-5'-O-isoleucyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-hexadecanoyl-5'-O-isoleucyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-stearoyl-5'-O-isoleucyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-eicosanoyl-5'-O-isoleucyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-docosanoyl-5'-O-isoleucyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-valyl-5'-O-dodecanoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-valyl-5'-O-tetradecanoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-valyl-5'-O-hexadecanoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-valyl-5'-O-stearoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-valyl-5'-O-eicosanoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,
1-(3'-O-valyl-5'-O-docosanoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,

1-(3'-O-isoleucyl-5'-O-dodecanoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,

1-(3'-O-isoleucyl-5'-O-tetradecanoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,

1-(3'-O-isoleucyl-5'-O-hexadecanoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,

1-(3'-O-isoleucyl-5'-O-stearoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,

1-(3'-O-isoleucyl-5'-O-eicosanoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,

1-(3'-O-isoleucyl-5'-O-docosanoyl)-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,

and their pharmaceutically acceptable salts.

Other preferred compounds include

9-((1-dodecanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)guanine,

9-((1-tetradecanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)guanine,

9-((1-hexadecanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)guanine,

9-((1-octadecanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)guanine,

9-((1-eicosanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)guanine,

9-((1-docasanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)guanine,

9-((1-dodecanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)guanine,

9-((1-tetradecanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)guanine,

9-((1-hexadecanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)guanine,

9-((1-octadecanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)guanine,

9-((1-eicosanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)guanine,

9-((1-docasanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)guanine,

2-amino-9-((1-dodecanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)purine,

2-amino-9-((1-tetradecanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)purine,

2-amino-9-((1-hexadecanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)purine,

2-amino-9-((1-octadecanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)purine,
2-amino-9-((1-eicosanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)purine,
2-amino-9-((1-docasanoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)purine,
2-amino-9-((1-dodecanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)purine,
2-amino-9-((1-tetradecanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)purine,
2-amino-9-((1-hexadecanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)purine,
2-amino-9-((1-octadecanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)purine,
2-amino-9-((1-eicosanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)purine,
2-amino-9-((1-docasanoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl)purine,
and their pharmaceutically acceptable salts.

Further preferred compounds include
3'-O-dodecanoyl, 5'-O-valyl-9-β-D-arabinofuranosylguanine,
3'-O-tetradecanoyl, 5'-O-valyl-9-β-D-arabinofuranosylguanine,
3'-O-hexadecanoyl, 5'-O-valyl-9-β-D-arabinofuranosylguanine,
3'-O-octadecanoyl, 5'-O-valyl-9-β-D-arabinofuranosylguanine,
3'-O-eicosanoyl, 5'-O-valyl-9-β-D-arabinofuranosylguanine,
3'-O-docosanoyl, 5'-O-valyl-9-β-D-arabinofuranosylguanine,
5'-O-dodecanoyl, 3'-O-valyl-9-β-D-arabinofuranosylguanine,
5'-O-tetradecanoyl, 3'-O-valyl-9-β-D-arabinofuranosylguanine,
5'-O-hexadecanoyl, 3'-O-valyl-9-β-D-arabinofuranosylguanine,
5'-O-octadecanoyl, 3'-O-valyl-9-β-D-arabinofuranosylguanine,
5'-O-eicosanoyl, 3'-O-valyl-9-β-D-arabinofuranosylguanine,
5'-O-docosanoyl, 3'-O-valyl-9-β-D-arabinofuranosylguanine,
3'-O-dodecanoyl, 5'-O-valyl-9-β-D-arabinofuranosylcytosine,
3'-O-tetradecanoyl, 5'-O-valyl-9-β-D-arabinofuranosylcytosine,
3'-O-hexadecanoyl, 5'-O-valyl-9-β-D-arabinofuranosylcytosine,
3'-O-octadecanoyl, 5'-O-valyl-9-β-D-arabinofuranosylcytosine,
3'-O-eicosanoyl, 5'-O-valyl-9-β-D-arabinofuranosylcytosine,
3'-O-docosanoyl, 5'-O-valyl-9-β-D-arabinofuranosylcytosine,
5'-O-dodecanoyl, 3'-O-valyl-9-β-D-arabinofuranosylcytosine,

5'-O-tetradecanoyl, 3'-O-valyl-9-β-D-arabinofuranosylcytosine,
5'-O-hexadecanoyl, 3'-O-valyl-9-β-D-arabinofuranosylcytosine,
5'-O-octadecanoyl, 3'-O-valyl-9-β-D-arabinofuranosylcytosine,
5'-O-eicosanoyl, 3'-O-valyl-9-β-D-arabinofuranosylcytosine,
5'-O-docosanoyl, 3'-O-valyl-9-β-D-arabinofuranosylcytosine,
and the corresponding isoleucyl analogues of each of the above.

The compounds of the invention, such as those of Formula I, Ia, Ib, Ic, I/II or mixed esters of phosphonylated antivirals can form salts which form an additional aspect of the invention. Appropriate pharmaceutically acceptable salts of the compounds of the invention include salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, isethionate, adipate, alginate, aspartate, benzoate, butyrate, digluconate, cyclopentanate, glucoheptanate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, proprionate, tartrate, lactobionate, pivolate, camphorate, undecanoate and succinate, organic sulphonic acids such as methanesulphonate, ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-napthalenesulphonate, benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate; and inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate, thiocyanate, persulphate, phosphoric and sulphonic acids. The compounds of Formula I, Ia, Ib, Ic, I/II etc may be isolated as the hydrate.

The compounds of the invention are particularly suited to oral administration, but may also be administered rectally, vaginally, nasally, topically, transdermally or parenterally, for instance intramuscularly, intravenously or epidurally. The compounds may be administered alone, for instance in a capsule, but will generally be administered in conjunction with a pharmaceutically acceptable carrier or diluent. The invention extends to methods for preparing a pharmaceutical composition comprising bringing a compound of Formula I, Ia, Ib, Ic, I/II or its pharmaceutically

acceptable salt in conjunction or association with a pharmaceutically acceptable carrier or vehicle.

Oral formulations are conveniently prepared in unit dosage form, such as capsules or tablets, employing conventional carriers or binders such as magnesium stearate, chalk, starch, lactose, wax, gum or gelatin. Liposomes or synthetic or natural polymers such as HPMC or PVP may be used to afford a sustained release formulation. Alternatively the formulation may be presented as a nasal or eye drop, syrup, gel or cream comprising a solution, suspension, emulsion, oil-in-water or water-in-oil preparation in conventional vehicles such as water, saline, ethanol, vegetable oil or glycerine, optionally with flavourant and/or preservative and/or emulsifier.

For antiviral use, the compounds of the invention may be administered at a daily dose generally in the range 0.1 to 200 mg/kg/day, advantageously, 0.5 to 100 mg/kg/day, more preferably 10 to 50mg/kg/day, such as 10 to 25 mg/kg/day. A typical dosage rate for a normal adult will be around 50 to 500 mg, for example 300 mg, once or twice per day for herpes infections and 2 to 10 times this dosage for HIV infections. In each case, regardless of whether the compound is an antiviral or anticancer compound, the appropriate dosage for the compound of the invention can be calculated by referring the pharmacokinetic performance of the present derivative relative to the established dosage regime of the parent compound by techniques well known in the pharmaceutical art.

As is prudent in antiviral therapy, the antiviral compounds of the invention can be administered in combination with other antiviral agents, such as acyclovir, valcyclovir, penciclovir, famciclovir, ganciclovir or foscarnet for herpes indications and AZT, ddI, ddC, d4T, 3TC, foscarnet, ritonavir, indinavir, saquinavir, delaviridine, Vertex VX 478, Agouron AG1343 and the like for retroviral

indications. Additional antivirals for hepatitis B indications include 2',3'-deoxy-3'-fluoroguanosine, lamivudine and various interferons.

The compounds of the invention can be prepared de novo or esterified from commercially available antivirals such as penciclovir or ganciclovir. The preparation of compounds where X is O, n is 1 and Y/Z define a ring can be prepared as described in WO 95/32983. The preparation of compounds wherein X is O, n is 0 and Y/Z define -C(OH)-, in particular arabinose compounds such as araC and araG are described in British patent application GB 1386584, EP 002192, German patent application no DE 2156637, international patent application no WO 9201456, Nucleosides Nucleotides (1982) 1(3) 233-7 & (1983), 2(3) 221-9, Synthesis (1978) (12) 908-910, J Heterocycl.Chem. (1988) 25(6) 1899-903 and Chattopadhaya et al, Nuc Acids Res (Spec Publ) (1978) and Tetrahedron Lett (1980) 21(5) 479-82.

The preparation of phosphonylated compounds is described in US 5 142 051, US 5 476 938 and J.Med Chem (1994) 37 1857-1864. Compounds where Y and Z together define a bond are described in Antiviral Res. 1994; Suppl 1:44 and J Med Chem (1990) 33 1281-1285. The preparation and esterification of ribavirin is described in WO 94/22887 and US 3984396 and the references cited therein.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" (John Wiley & Sons, New York, 1981), which is hereby incorporated by reference. N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoracetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl

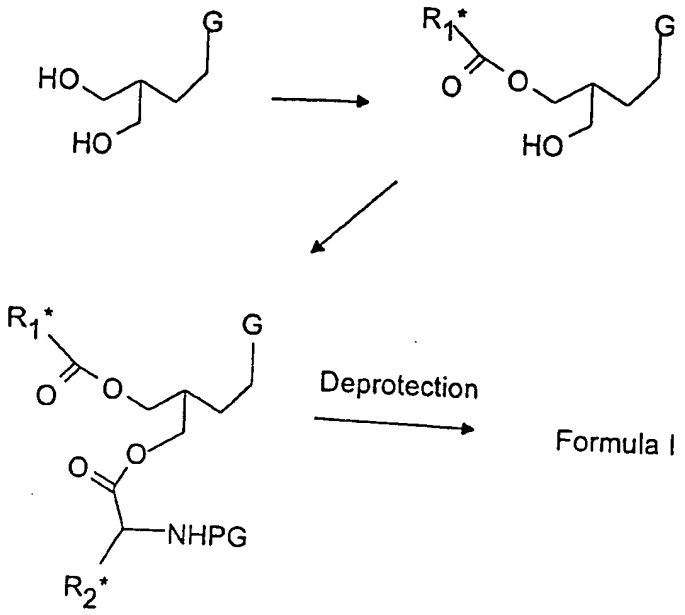
groups such as benzenesulfonyl, p-toluenesulfonyl, and the like, carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butoxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Favoured N-protecting groups include trityl, phenylsulfonyl, benzyl, t-butoxycarbonyl (BOC) and benzyloxycarbonyl (CBz).

Hydroxy and/or carboxy protecting groups are also extensively reviewed in Greene ibid and include ethers such as methyl, substituted methyl ethers such as methoxymethyl, methylthiomethyl, benzyloxymethyl, t-butoxymethyl, 2-methoxyethoxymethyl and the like, silyl ethers such as trimethylsilyl (TMS), t-butyldimethylsilyl (TBDMS) tribenzylsilyl, triphenylsilyl, t-butyldiphenylsilyl triisopropyl silyl and the like, substituted ethyl ethers such as 1-ethoxymethyl, 1-methyl-1-methoxyethyl, t-butyl, allyl, benzyl, p-methoxybenzyl, diphenylmethyl, triphenylmethyl and the like, aralkyl groups such as trityl, and pixyl (9-hydroxy-9-phenylxanthene derivatives, especially the chloride). Ester hydroxy protecting groups include esters such as formate, benzylformate, chloroacetate, methoxyacetate, phenoxyacetate, pivaloate, adamantoate, mesitoate, benzoate and the like.

The bases in these start materials, such as the 2-amino group of guanine or the carboxamide group of ribavirin derivatives are optionally protected with a

conventional protecting group such as acetyl BOC (t-BuO-CO-), Z or CBz (BnO-CO-) or Ph_3C-. Fmoc may be useful for cytosine. The compounds of Formula I may be prepared from such start materials as described below:

Scheme A-1. Direct acylation method



The direct acylation method is particularly suitable for achiral or symmetric compounds such as penciclovir or ganciclovir. Scheme A above depicts the acylation of a penciclovir derivative in which G is guanine or 6-deoxyguanine, PG is an optional protecting group or hydrogen, R_1* is the fatty acid chain and R_2* is the valine, isoleucine, leucine, alanine etc side chain. The nucleoside (derivative) preferably reacts in the first step with an activated R_1 fatty acid derivative, as further described below, in a solvent such as dimethylformamide or pyridine, to give a monoacylated product. Acylating first with the fatty acid, rather than the amino acid is convenient as the lipophilic nature of the acyl facilitates subsequent handling.

After purification, the R_1 monoacylated compounds are further acylated in the R_2 position with the appropriate activated amino acid derivative to give diacylated products using similar procedures as for the first esterification step. The R_1 α-amino acid may be suitably N-protected with N-BOC, Fmoc, N-CBz or the like. The diester products are subsequently subjected to a conventional deprotection treatment using for example trifluoroacetic acid,

HCl(aq)/dioxane or hydrogenation in the presence of catalyst to give the desired compound of Formula I. The compound may be in salt form depending on the deprotection conditions.

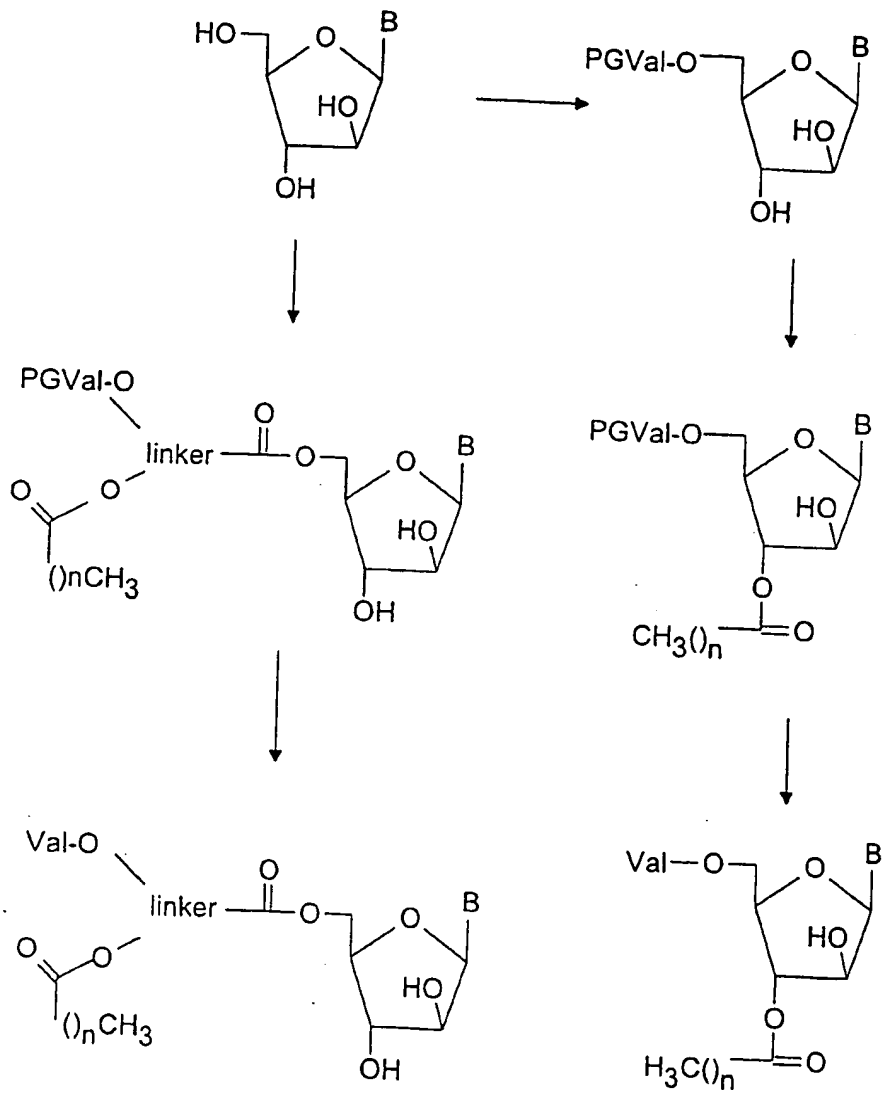
In Scheme A-1 the fatty acid ester has been acylated to the nucleoside first, but it will be apparent that it is also feasible to acylate with the amino acid ester first, as shown in scheme A-2.

The activated R_1/R_2 acid derivative used in the various acylations may comprise e.g. the acid halide, acid anhydride, activated acid ester or the acid in the presence of coupling reagent, for example dicyclohexylcarbodiimide, where "acid" in each case represents the corresponding R_1 amino acid or the R_2 fatty acid. Representative activated acid derivatives include the acid chloride, formic and acetic acid derived mixed anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinamide derived esters, N-hydroxyphthalimide derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like.

In cases where the nucleoside is chiral or where the hydroxy groups are not identical it is possible to preferentially direct the first acylation to a particular hydroxy group with careful control of the reaction conditions, for example, by manipulating the reagent concentrations or rate of addition, especially of the acylating agent, by lowering the temperature or by the choice of solvent. The reaction can be followed by TLC to monitor the controlled conditions.

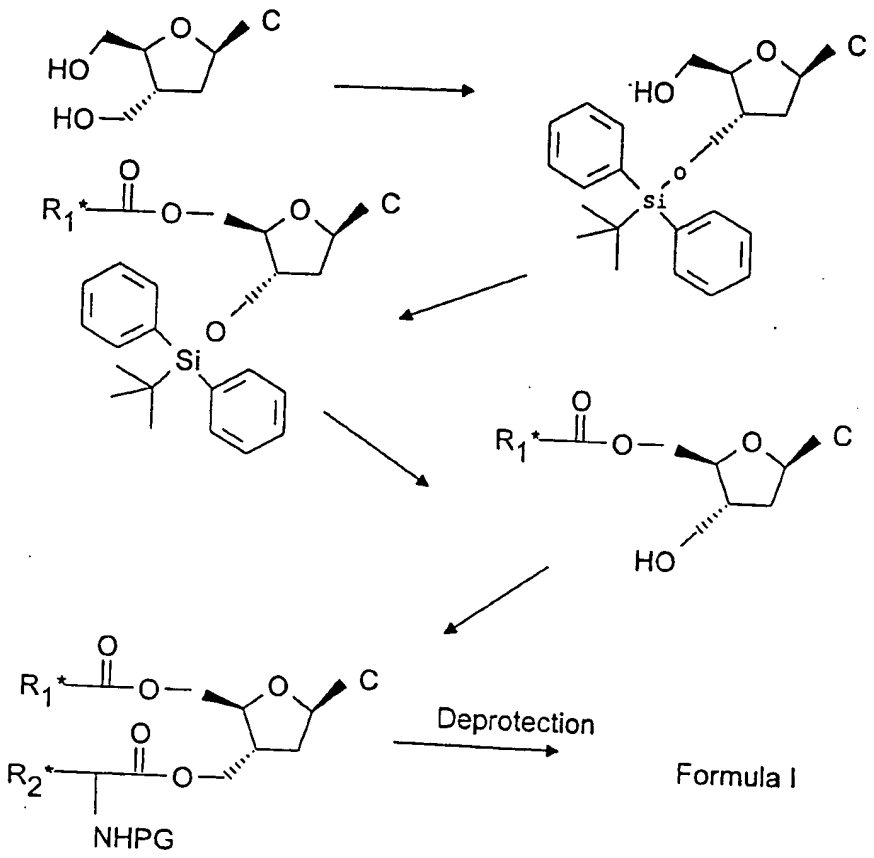
SchemeA-2 below shows that the 5-hydroxy group of arabinose nucleosides is preferentially acylated, either with a fatty acid or aliphatic amino acid ester or with a linker group, such as those of formula II.

Scheme A-2. Hydroxyls of differential reactivity



In scheme A-2, the greater reactivity of the primary hydroxyl allows the linker or first acylation of R_1/R_2 to be preferentially directed there, without requiring protection of the secondary hydroxyl groups. The rightmost series shows the addition of the amino acid ester first, but the fatty acid ester could alternatively be introduced first at this primary hydroxyl.

B. Via protection of an hydroxy group:



Formula I

wherein C is (optionally N-protected) cytosine and R_1* and R_2* etc are as described for scheme A. This technique is particularly suitable for chiral or asymmetric nucleosides where it is desired to direct the fatty acid and amino acid esters to specified hydroxy groups.

Scheme B relies on regioselective protection of one of the hydroxy groups with a bulky protecting group. In scheme B above this is depicted as t-butyldiphenylsilyl, but other regioselective protecting groups such as trityl, 9-(9-phenyl)xanthenyl, 1,1-bis(4-methylphenyl)-1'-pyrenylmethyl may also be appropriate. The 2'-hydroxy group, if present, will generally be sufficiently shielded by the base, but may also be protected with a conventional hydroxy

protecting group. The resulting product is acylated at the free hydroxy group using analogous reagents and proccdures as described in scheme A above, but wherein the activated acid derivative is the R_1 fatty acid, for example, myristic, stearic, oleic, elaidic acid chloride, etc. The thus monoacylated compounds are subjected to appropriate deprotection treatment to remove the protecting group which can be done in a highly selective manner with such reagents, depending on the regioselective protecting group, as HF/pyridine and thc likc and manipulation of the reaction conditions, viz. reagent concentration speed of addition, temperature and solvent etc, as elaborated above. The now free hydroxy position is acylated with the activated α-amino acid in a similar way as described in scheme A above.

Additional techniques for introducing the amino acid ester in the above scheme A or B include the 2-oxo-4-aza-cycloalkane-1,3-dione method described in international patent application no WO 94/29311.

Alternatively, the common linking group, such as those of the formula II with the R^3 and R^4 fatty acid and amino acids already acylated thereon can be introduced to the nucleoside derivative using generally similar directed esterification/carbonyl/amide bonding techniques in conjunction with Scheme A or Scheme B above. It will be generally necessary to protect the free amino group on the amino acid ester with conventional protecting groups such as CBz or BOC.

Esterification of the phosphonylated antivirals with the R^1 and R^2 groups linked via an intermediate -CH(R^a)O- group proceeds as described in J.Med Chem. 37 1857-1864 (1994), but wherein the stepwise esterification as per schemes A and B is employed, preferably with the corresponding activated acyloxyalkyl, optionally using protecting groups such as benzyl on free hydroxy groups. Preferably R^a is methyl thereby producing a non-toxic ethanol metabolite.

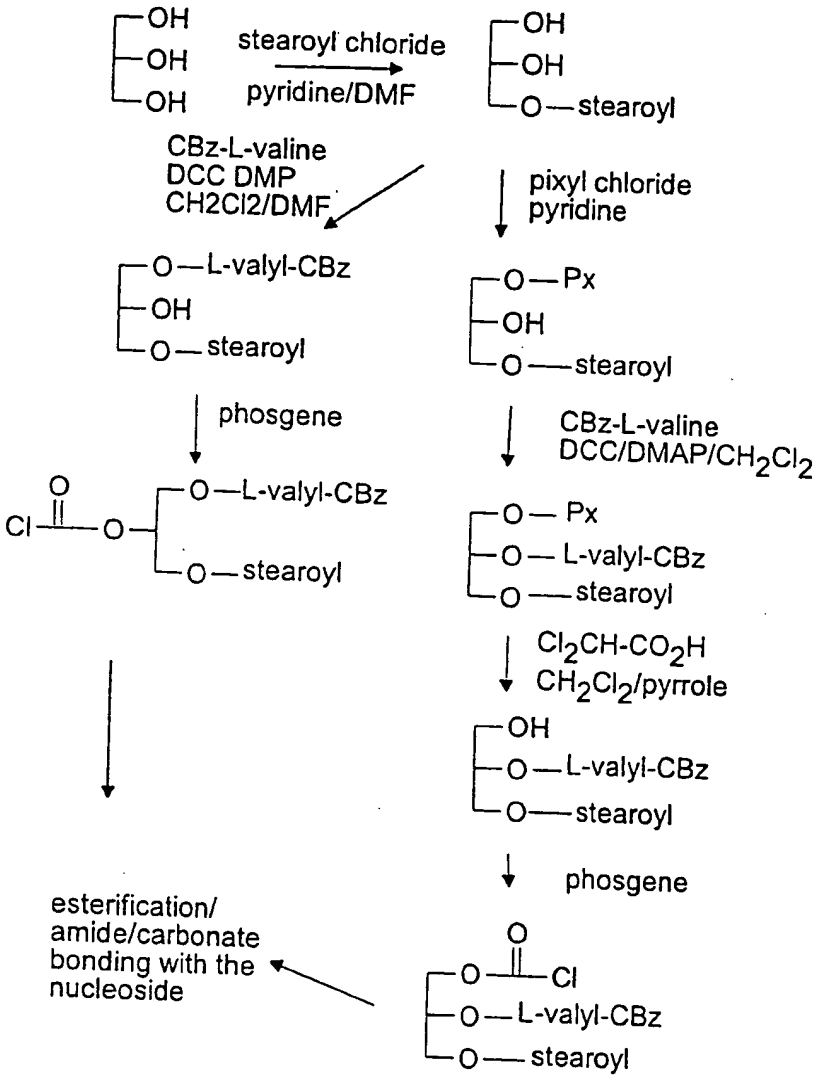
Compounds wherein Y comprises a -C(OH)- group can theoretically be acylated with R_1, R_2 or a structure of the formula II at the 2'-position thus defined. However the base will generally sterically shield the 2'-hydroxy position, requiring robust protecting groups for the 3', 5' and/or base in conjunction with moderatly strong acylating conditions.

The common linking group of Formula II can be introduced to the 3' or 5' position or, less favourably the 2' position, using generally similar directed esterification/carbonate/amide bonding techniques as Scheme A or Scheme B above in conjunction with the corresponding activated derivative of Formula II and appropriate protection of the non-participating hydroxy function on the sugar or acyclic moiety.

Compounds prepared in any of the above techniques can be post-modified as in conventional nucleoside chemistry. This will generally require protection of the amino function of the amino acid ester with a protecting group such as BOC.

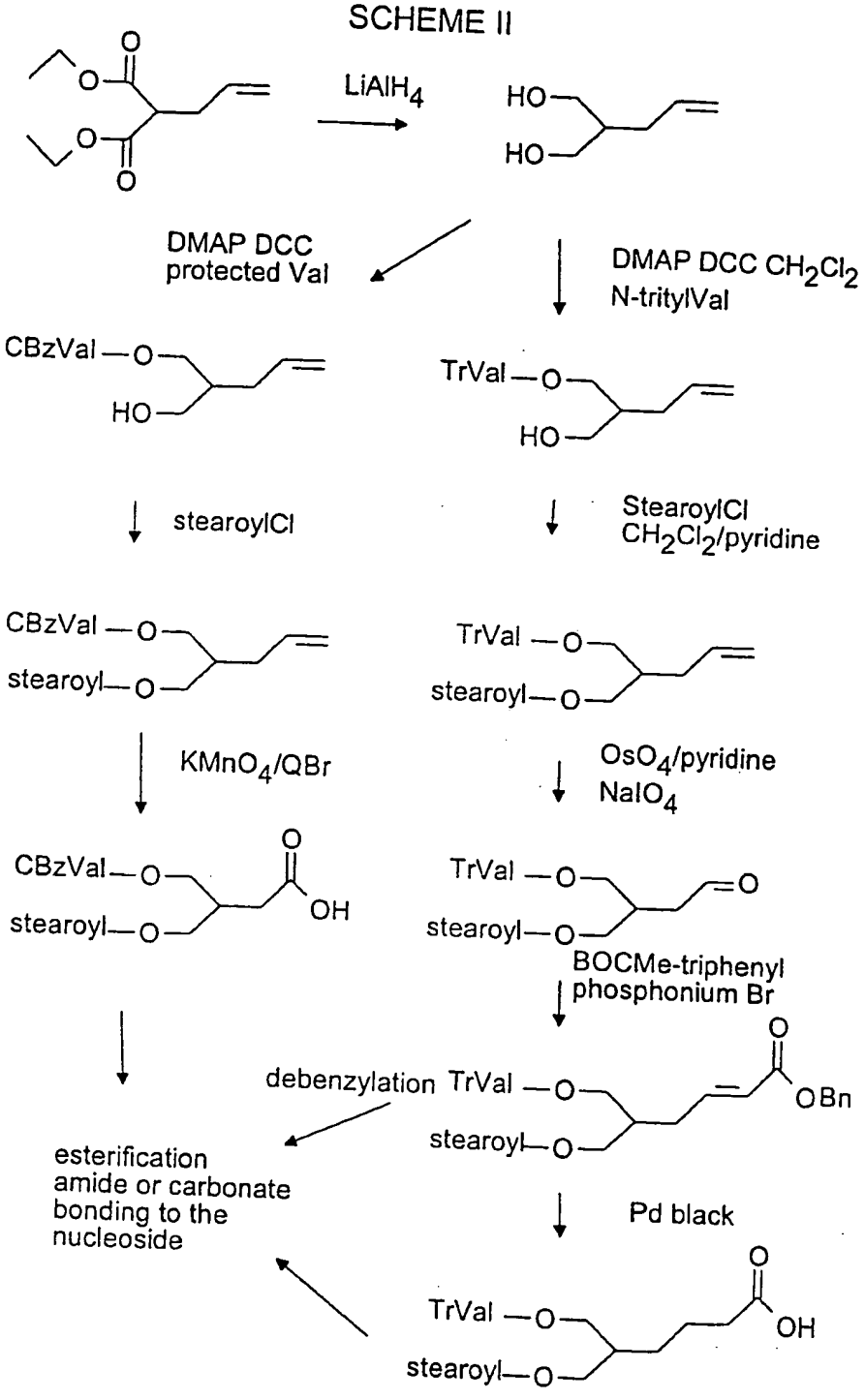
Common linker groups of the formula II wherein m is 1 and m' is 0 can be prepared from glycerol by regioselectively esterifying R_3 and R_4 to positions 1 and 2 of the glycerol, as depicted below in scheme 1, followed by conversion of the hydroxy at position 3 to the appropriate -T-C(=O)-group. The leftmost series of reactions on Scheme 1 shows the situation where R_3 is esterified to position 1 of the glycerol and R_4 is esterified to position 3. The corresponding arrangement where R_4 is esterified to position 2 and R_3 to position 1 can be achieved by first treating the glycerol with CBz-L-valine/DCC/DMAP/DMF and then protecting the 3 position with pixyl chloride prior to esterifying the fatty acid to position 2 of the glycerol, deprotecting and converting the 3 position as necessary.

SCHEME I



Although Scheme 1 has been illustrated by reference to a combination wherein R_3 is stearoyl and R_4 is L-valyl, it will be appreciated that this basic scheme will also be applicable to derivatives of other fatty acids and amino acids or where R_4 is the fatty acid ester and R_3 the amino acid ester. Linkers where T comprises an -NH- group can be prepared by analogous regioselective esterification followed by conversion of the free hydroxyl to azide, reduction to amine and reaction with phosgene to form the corresponding chlorocarbamate.

SCHEME II



Linkers where m is 1, n is alkylene or alkenylene and T is a bond can be prepared as shown in Scheme II above. Other permutations of m, m' and n etc in the linker

group of formula II can be prepared analagously to the above with the corresponding starter materials, such as 1,2,4-trihydroxybutane (CA registry number 3968-00-6), 3,4-dihydroxybutanoic acid (1518-61-2 & 22329-74-4), (S)-3,4-dihydroxybutanoic acid (51267-44-8), (R)-3,4-dihydroxybutanoic acid (158800-76-1), 1,2,5-pentanetriol (51064-73-4 & 14697-46-2), (S)-1,2,5-pentanetriol (13942-73-9), (R)-1,2,5-pentanetriol (171335-70-9), 4,5-dihydroxypentanoic acid (66679-29-6 & 129725-14-0), 1,3,5-pentanetriol (4328-94-3) and 3-(2-hydroxyethyl)-1,5-pentanediol (53378-75-9). The preparation of each of these starting materials is described in the references to the respective registry number.

Futher linker structures of Formula II, and their placement via acylation or carbonate bonding onto nucleoside analogues are shown in the following examples.

A further aspect of the invention thus provides a method for the preparation of the compounds of first aspect of the invention comprising

a) optionally protecting the base of a compound of formula I wherein R_1 and R_2 are each hydrogen,

b) regioselectively reacting the compound of Formula 1 at position R_1 or R_2 by either

i) acylating with an optionally protected aliphatic amino acid group or a C_5-C_{21}COOH derivative; or

ii) protecting with a regioselective protecting group;

c) acylating at the other of positions R_1 or R_2 with a C_5-C_{21}COOH derivative or an aliphatic amino acid;

d) replacing the regioselective protecting group at R_1/R_2, if present, with an optionally protected aliphatic amino acid acyl or a C_5-C_{21}COOH derivative; and

e) deprotecting the resulting compound as necessary.

The acylation at step b) or the replacement at step d) may comprise the placement of the amino acid ester via a 2-oxo-4-aza-(5-isopropyl or 5-isobutyl)-cycloalkane-1,3-dione derivative.

A further aspect of the invention provides a method for the preparation of the alternative compounds of the invention comprising

a) optionally protecting the base of a compound of formula I wherein R_1 and R_2 are each hydrogen,

b) regioselectively reacting the compound of Formula 1 at position R_1 or R_2 by either

i) acylating/carbonate bonding/amide bonding an activated structure of the formula II; or

ii) protecting with a regioselective protecting group;

c) replacing the regioselective protecting group at R_1/R_2, if present, by acylating/carbonate bonding/amide bonding an activated structure of the formula II; and

d) deprotecting the resulting compound as necessary.

Detailed Description of the Invention

The invention will now be illustrated by way of example only with reference to the following non-limiting Examples.

EXAMPLE 1

9-(1-Stearoyloxy-3-(L-valyloxy)-2-propoxy)methyl guanine:

i) Preparation of 9-(1-Stearoyloxy-3-hydroxy-2-propoxy)-methyl)guanine.

To a solution of 9-(1,3-dihydroxy-2-propoxy)-methyl)guanine (1.02 g, 4 mmole) in DMF (120 ml) was added pyridine (1.3 ml, 16 mmole). Subsequently, stearoyl chloride (1.62 g, 4.8 mmole) was added to the reaction mixture portionwise. The reaction was kept overnight, and an additional portion of stearoyl chloride (241 mg, 0.8 mmole) was added. After 3 h, methanol (3 ml) was added to the reaction mixture and temperature was raised to 45°C. The reaction was kept at this temperature for 2 h. The mixture was evaporated *in vacuo* and the product was isolated by silica gel column chromatography (1.17 g)

^{1}H-NMR (DMSO-d6): 10.6 (s, 1H, NH), 7.78 (s, 1H, H-8), 6.58 (s, 2H NH_2), 5.40 (s, 2H, CH_2), 3.96 (m, 2H, CH_2), 3.82 (m, 1H, CH), 3.39 (m, 2H), 2.10 (t, 2H, stear), 1.40 (m, 2H, stear), 1.23 (m, 28H, stear), 0.88 (t, 3H, stear).

ii) Synthesis of 9-((1-Stearoyloxy-3-(N-t-butoxycarbonyl-L-valyloxy)-2-propoxy)-methyl)guanine:

To a solution of 9-((1-Stearoyloxy-3-hydroxy-2-propoxy)-methyl)guanine (521 mg, 1 mmole) and N-t-butoxycarbonyl-L-valine (651 mg, 3 mmole) in DMF (20 ml) was added 4-dimethylaminopyridine (18.3 mg, 0.15 mmole) and DCC (618 mg, 3 mmole). The reaction was kept overnight and then filtered through Celite. The filtrate was diluted with dichloromethane and then washed with aqueous sodium hydrogen carbonate solution. the organic phase was concentrated *in vacuo* and the product was isolated by silica gel column chromatography. (217 mg).

^{1}H-NMR (DMSO-d6): 10.62 (s, 1H, NH), 7.80 (d, 1H, H-8), 6.47 (s, 2H, NH_2), 5.40 (s, 2H, CH_2), 4.04 (m, 6H), 2.10 (m, 2H, stear), 1.95 (m, 1H), 1.67 (m, 2H), 1.36 (s, 9H, Boc), 1.22 (m, 28H, stear), 0,84 (m, 9H).

iii) Synthesis of 9-((1-stearoyloxy-3-(L-valyloxy)-2-propoxy)-methyl)guanine:

9-((1-Stearoyloxy-3-(-N-t-butoxycarbonyl-L-valyloxy)-2-propoxy)-methyl) guanine (200 mg, 0.277 mmolc) was treated with trifluoroacetic acid (5 ml) at 0°C for 20 min and then the reaction mixture was evaporated *in vacuo*. The residue was successively coevaporated with toluene, methanol, and freeze-dried to give the desired product (237 mg).

^{1}H-NMR (DMSO-d6): 10.4 (s, 1H, NH), 8.40 (b, 3H, NH_3), 7.96 (d, 1H, H-8), 5.45 (s, 2H, CH_2), 4.11 (m, 6H), 2.27 (m, 2H), 2.03 (m, 1H, Val), 1.46 (m, 2H), 1.20 (m, 9H).

EXAMPLE 2

9-((1-Stearoyloxy-3-(L-alanyloxy)-2-propoxy)-methyl) guanine:

i) Synthesis of 9-((1-Stearoyloxy-3-(-N-t-butoxycarbonyl-L-alanyloxy)-2-propoxy)-methyl) guanine:

To a solution of 9-((1-Stearoyloxy-3-hydroxy-2-propoxy)-methyl)guanine (365 mg, 0.7 mmole) and N-t-butoxycarbonyl-L-alanine (396 mg, 2.1 mmole) in DMF (15 ml) was added 4-dimethylaminopyridine (12 mg, 0.1 mmole) and DCC (432 mg, 2.1 mmolc). The reaction was kept overnight and then filtered through Celite. The filtrate was diluted with dichloromethane and then washed with aqueous sodium hydrogen carbonate solution. The organic phase was concentrated *in vacuo* and the product was isolated by silica gel column chromatography. Yield: 164 mg.

^{1}II-NMR (DMSO-d6): 10.61 (s, 1H, NH), 7.81 (s, 1H, H-8), 6.48 (s, 2H, NH_2), 5.41 (s, 2H, CH_2), 4.04 (m, 6H), 2.10 (t, 2H, stear), 1.35 (m, 11H), 1.22 (m, 31H), 0.85 (t, 3H, stear).

iii) Synthesis of 9-((1-Stearoyloxy-3-(L-alanyloxy(-2-propoxy)-methyl) guanine:

9-((1-Stearoyloxy-3-(N-t-butoxycarbonyl-L-alanyloxy)-2-propoxy)-methyl) guanine (150 mg, 0.21 mmole) was treated with trifluoroacetic acid (5 ml) at 0°C for 30 min and then the reaction mixture was evaporated *in vacuo*. The residue was successively coevaporated with toluene, methanol, and freeze-dried to give the desired product (177 mg).

^{1}H-NMR (DMSO-d6): 10.77 (s, 1H, NH), 8.30 (b, 3H, NH_3), 7.93 (d, 1H, H-8), 4.11 (m, 6H), 2.15 (t, 2H, stear), 1.42 (m, 2H), 1.23 (m, 31H), 0.85 (t, 3H, stear).

EXAMPLE 3

9-(1-Stearoyloxy-3-(L-isoleucyloxy-2-propoxy)-methyl) guanine:

i) Synthesis of 9-(1-Stearoyloxy-3-(-N-t-butoxycarbonyl-L-isoleucyloxy)-2-propoxy)-methyl) guanine:

To a solution of 9-(1-Stearoyloxy-3-hydroxy-2-propoxy)-methyl guanine (365 mg, 0.7 mmole) and N-t-butoxycarbonyl-L-isoleucine (485 mg, 2.1 mmole) and DCC (432 mg, 2.1 mmole). The reaction was kept overnight and then filtered through Celite. The filtrate was diluted with dichloromethane and then washed with aqueous sodium hydrogen carbonate solution. The organic phase was concentrated *in vacuo* and the product was isolated by silica gel column chromatography. Yield: 208 mg.

^{1}H-NMR (DMSO-d6): 10.61 (s, 1H, NH), 7.80 (d, 1H, H-8), 6.47 (b, 2H, NH_2), 5.40 (s, 2H, CH_2), 4.01 (m, 6H), 2.11 (m, 2H), 1.58 (m, 1H, Ile), 1.36 (m, 11H), 1.23 (m, 28H), 0.81 (m, 9H).

ii) Synthesis of 9-(1-Stearoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl) guanine:

9-(1-Stearoyloxy-3-(-N-t-butoxycarbonyl-L-isoleucyloxy)-2-propoxy)-methyl) guanine (190 mg, 0.26 mmole) was treated with trifluoroacetic acid (5 ml) at 0°C for 20 min and then the reaction mixture was evaporated *in vacuo*.

The residue was successively coevaporated with toluene, methanol, and freeze-dried to give desired product (225 mg).

^{1}H-NMR (DMSO-d6): 10.77 (s, 1H, NH), 7.91 (d, 1H, H-8), 6.55 (b, 2H, NH_2), 5.44 (s, 2H, CH_2), 4.12 (m, 6H), 2.16 (m, 2H, stear). 1.78 (m, 1H, Ile), 1.42 (m, 2H), 1.23 (m, 28H), 0.84 (m, 9H).

EXAMPLE 4

9-[4-Stearoyloxy-3-(L-valyloxymethanyl)butyl] guanine:

i) Synthesis of 9-(4-Stearoyloxy-3-hydroxymethyl-butyl) guanine:
To a solution of 9-(4-hydroxy-3-hydroxymethyl-butyl) guanine (1.01 g, 4 mmole) in DMF (120 ml) was added pyridine (1 ml, 11 mmole). Subsequently, stearoyl chloride (1.51 g, 5 mmole) was added to the reaction mixture. The reaction was kept overnight, and was then diluted with dichloromethane. The mixture was washed with aqueous sodium hydrogen carbonate solution. The organic phase was evaporated *in vacuo* and the product was isolated by silica gel column chromatograpy. 1.22 g.

^{1}H-NMR (DMSO-d6): 7.68 (s, 1H, H-8), 6.60 (b, 2H, NH_2), 4.05 (m, 6H), 2.23 (t, 2H), 1.75-1.40 (m, 5H), 1.20 (m, 28H), 0.83 (t, 3H).

ii) Synthesis of 9-(4-Stearoyloxy-3-(N-t-butoxycarbonyl-L-valyloxymethyl)butyl) guanine:
To a solution of 9-(4-Stearoyloxy-3-hydroxymethyl-butyl) guanine (519 mg, 1 mmole) and N-t-butoxycarbonyl-L-valine (651 mg, 3 mmole) in DMF (20 ml) was added 4-dimethylaminopyridine (18.3 mg, 0.15 mmole) and DCC (618 mg, 3 mmole). The reaction was kept 5 h and filtered through Celite. The filtrate was diluted with dichloromethane and then washed with aqueous sodium hydrogen carbonate solution. The organic phase was concentrated *in vacuo* and the product was isolated by silica gel column chromatograpy. 239 mg.

^{1}H-NMR (DMSO-d6): 10.58 (s, 1H, NH), 7.68 (s, 1H, H-8), 6.49 (b, 2H, NH_2), 4.03 (m, 6H), 3.82 (m, 1H), 2.38 (t, 2H), 1.80 (m, 4H), 1.50 (m, 2H), 1.32 (m, 9H), 1.22 (m, 28H), 0.82 (m, 9H).

iii) Synthesis of 9-(4-Stearoyloxy-3-(L-valyloxymethyl)butyl) guanine:

9-(4-Stearoyloxy-3-(N-t-butoxycarbonyl-L-valyloxymethyl)butyl guanine (225 mg, 0.312 mmole) was treated with trifluoroacetic acid (5 ml) at 0°C for 40 min and then the reaction mixture was evaporated *in vacuo*. The residue was successively coevaporated with toluene, methanol, and freeze-dried to give the desired product (266 mg).

^{1}H-NMR (DMSO-d6): 10.85 (s, 1H, NH), 8.31 (b, 3H, NH_3), 8.06 (s, 1H, H-8), 4.08 (m, 7H), 2.28 (t, 2H), 2.12 (m, 1H), 1.99 (m, 1H), 1.82 (m, 2H), 1.50 (m, 2H), 1.23 (m, 28H), 0.92 (m, 6H), 0.85 (t, 3H).

EXAMPLE 5

9-((4-Stearoyloxy-3-(L-alanyloxymethyl)butyl) guanine:

i) Synthesis of 9-(4-Stearoyloxy-3-(-N-t-butoxycarbonyl-L-anlanyloxymethyl)butyl) guanine:

To a solution of 9-(4-Stearoyloxy-3-(hydroxymethyl)butyl) guanine (200 mg, 0.38 mmole) and N-t-butoxycarbonyl-L-alanine (218 mg, 1.15 mmole) in DMF (6 ml) was added 4-dimethylaminopyridine (7 mg, 0.06 mmole) and DCC (238 mg, 1.15 mmole). The reaction was kept for 3 h and then filtered through Celite. The filtrate was diluted with dichloromethane and then washed with aqueous sodium hydrogen carbonate solution. The organic phase was concentrated *in vacuo* and the product was isolated by silica gel column chromatograpy. Yield: 98 mg.

^{1}H-NMR ($CDCl_3$+CD_3OD): 7.57 (d, 1H, H-8), 4.10 (m, 7H), 2.33 (t, 2H), 2.05 (m, 1H), 1.90 (m, 2H), 1.61 (m, 2H), 1.45 (s, 9H), 1.38 (d, 3H), 1.30 (m, 28H), 0.89 (t, 3H).

ii) Synthesis of 9-((4-Stearoyloxy-3-(L-alanyloxymethyl)butyl guanine:
9-(4-Stearoyloxy-3-(-N-t-butoxycarbonyl-L-alanyloxymethyl)butyl guanine (90 mg, 0.13 mmolc) was treated with trifluoroacetic acid (3 ml) at 0°C for 50 min and then the reaction mixture was evaporated *in vacuo*. The residue was successively coevaporated with toluene, methanol, and freeze-dried to give the desired product (100 mg).

^{1}H-NMR (DMSO-d6): 10.78 (s, 1H, NH), 8.30 (b, 3H, NH_3), 8.01 (s, 1H, H-8), 6.53 (b, 2H, NH_2), 4.10 (m, 7H), 2.30 (t, 2H), 1.97 (m, 1H), 1.80 (m, 2H), 1.49 (m, 2H), 1.32 (q, 3H), 1.23 (m, 28H), 0.83 (t, 3H).

EXAMPLE 6

9-(4-Stearoyloxy-3-(L-isoleucyloxymethyl)butyl) guanine:

i) Synthesis of 9-(4-Stearoyloxy-3-(-N-t-butoxycarbonyl-L-isoleucyloxymethyl)butyl) guanine:
To a solution of 9-(4-Stearoyloxy-3-(hydroxymethyl)butyl) guanine (200 mg, 0.38 mmole) and N-t-butoxycarbonyl-L-isoleucine (263 mg, 1.15 mmole) in DMF (5 ml was addcd 4-dimethylaminopyridine (7 mg, 0.06 mmole) and DCC (237 mg, 1.15 mmole). The reaction was kept for 3 h and an additional portion of DCC (118 mg, 0.57 mmole) was added. After reaction overnight, it was filtered through Celite. The filtrate was diluted with dichloromethane and then washed with aqueous sodium hydrogen carbonate solution. the organic phase was concentrated *in vacuo* and the product was isolated by silica gel column chromatography. Yield: 201 mg.

^{1}H-NMR (DMSO-d6): 10.51 (s, 1H, NH), 7.68 (s, 1H, H-8), 6.40 (b, 2H, NH_2), 4.05 (m, 6H), 3.82 (t, 1H), 2.37 (t, 2H), 1.95 (m, 2H), 1.83 (m, 2H), 1.48 (m, 2H), 1.36 (m, 9H), 1.25 (m, 28H), 0.82 (m, 9H).

ii) Synthesis of 9-(4-stearoyloxy-3-(L-isoleucyloxymethyl)butyl) guanine:

9-(4-Stearoyloxy-3-(N-t-butoxycarbonyl-L-isoleucyloxymethyl)butyl) guanine (190 mg, 0.26 mmole) was treated with trifluoroacetic acid (5 ml) at 0°C for 50 min and then the reaction mixture was evaporated *in vacuo*. The residue was successively coevaporated with toluene, methanol, and freeze-dried to give the desired product (217 mg).

^{1}H-NMR (DMSO-δ6): 10.93 (s, 1H, NH), 8.34 (b, 3H, NH_3), 8.12 (s, 1H, H-8), 6.66 (b, 2H, NH_2), 4.08 (m, 6H), 3.95 (m, 1H), 2.50 (t, 2H), 2.18 (m, 1H), 1.98 (m, 1H), 1.86 (m, 2H), 1.48 (m, 2H), 1.22 (m, 28H), 0.87 (m, 6H), 0.84 (t, 3H).

EXAMPLE 7
3'-O-stearoyl-5'-O-valyl-ribavirin

Boc-Val-OH (5.47 g; 25.2 mmol) and DCC (3.05 g; 14.8 mmol) in CH_2Cl_2 (240 mL) were stirred for 3 h at room temperature under nitrogen. The mixture was filtrated and the solvent was evaporated. The anhydride was dissolved in DMF (300 mL). Ribavirine (3.0 g; 12.3 mmol) and DMAP (226 mg; 1.85 mmol) were added to this solution and it was stirred for 24 h at room temperature. DMF was evaporated and the residue was purified by chromatography on silica gel by eluting with MeOH/CH_2Cl_2 5/95 to give 2.5 g of 5'-Boc-valine-ribavirin.

1H NMR (250 MHz, DMSO) δ 8.90 (s, 1H), 7.87 (br s, 1H), 7.66 (br s, 1H), 7.20 (d, 1H), 5.88 (m, 2H),5.20 (m, 1H), 5.24 (t, 1H), 4.72 (m, 1H), 4.10 (m, 1H), 4.02 (m, 1H), 3.57 (m, 2H), 2.10 (m, 1H), 1.37 (s, 9H), 0.91 (t, 3H).

Stearoyl chloride (1.34 g; 4.4 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a solution of the intermediate above (2.17 g; 4.9 mmol) in pyridine (60 mL) on ice. The mixture was stirred for 15 min at the same temperature, and then the cooling was withdrawn. The stirring was continued for 2 h. The mixture was treated with 1M $NaHCO_3$, and the organic layer was washed with H_2O and brine, and dried over Na_2SO_4. The solution was concentrated and purified by chromatography on silica gel by eluting with CH_2Cl_2, 2.5 % MeOH in CH_2Cl_2 and 5 % MeOH in CH_2Cl_2 to

give 0.6 g of product which was deprotected with TFA (20 mL) on ice under 2 h to give after evaporating and drying in vacuum 560 mg of 3'-O-stearoyl, 5'-O-valyl-ribavirin.

1H NMR (250 MHz, DMSO) δ 8.89 (s, 1H), 8.53 (br s, 2H), 7.87 (br s, 1H), 7.71 (br s, 1H), 6.01 (d, 1H), 5.43 (t, 1H), 4.78 (t, 1H), 4.42-4.02 (m, 4H), 2.40-2.10 (m, 3H), 1.46 (m, 2H), 1.23 (br s, 28H), 1.02 (t, 6H), 0.84 (t, 3H).

EXAMPLE 8

3'-O-stearoyl-5'-O-valyl-arabinocytosine

a) N-(benzyloxycarbonyl)araC.

A mixture of araC (243 mg; 1.00 mmol), trimethylchlorosilane (1.00 g; 9.2 mmol), N,N-dimethylformamide (1 ml), and pyridine (6 ml) was stirred for 1h at room temperature and then cooled to -15°C in an ice-salt bath. A 50% solution of benzyl chloroformate (680 mg; 2.0 mmol) in toluene was added in 3 portions beneath the surface of the reaction mixture, which was kept at room temperature for 0.5h and then cooled in ice-water. Water (5 ml) was added (very slowly initially), then 5 ml of ethyl acetate. After stirring for ten minutes, the aqueous phase was extracted with 5x5 ml of ethyl acetate, and the combined organic phases were evaporated to small volume. The crude product was purified by chromatography on 8 g of silica gel, using ethyl acetate + methanol + water (15+2+1) as eluent with slight warming of the column to prevent crystallization. Yield of title compound was 267 mg (71%).

^{13}C NMR ($CDCl_3$, 62.975 MHz): δ 171.9 (COO); 162.6 (C4); 156.7 (C2); 156.3 (CONH-Val); 152.4 (CONH-4); 146.3 (C6); 136.0 (Ph-C1-Val); 134.9 (Ph-C1-cyt); 128.4-128.0 (2 Ph); 95.1 (C5); 88.9 (C1'); 83.3 (C4'); 77.1 (C3'); 75.0 (C2'); 67.8 (Ph CH_2-Val); 67.0 (Ph CH_2-cyt); 64.7 (C5'); 59.5 (Val-aC); 31.5 (Val-bC); 19.0/18.8 and 17.9/17.7 (Val 2 CH_3).

b) N-(benzyloxycarbonyl)-5'-(N-benzyloxycarbonyl-L-valyl)araC.

A mixture of N-benzyloxycarbonyl-L-valine (302 mg; 1.20 mmol), dicyclohexylcarbodiimide (136 mg; 0.66 mmol), and 4-dimethylaminopyridine (10 mg; 0.08 mmol) in dichloromethane (3 ml) was stirred at room temperature for 1h, filtered and evaporated in vacuum to small volume to yield crude N-benzyloxycarbonyl-L-valine anhydride. The intermediate of step a) (174 mg; 0.46 mmol), triethylamine (100 mg; 1.0 mmol), 4-dimethylaminopyridine (10 mg; 0.08 mmol) and N,N-dimethylformamide (2 ml) were added and the mixture was stirred at room temperature. A few minutes later, the new product could be detected by TLC. After 2h the mixture was evaporated in vacuum to small volume and purified on a silica gel column (8 g; ethyl acetate + methanol + water, 15+2+1). The first fractions contained lipophilic byproducts, then the pure title compound was eluted (yield 97.5 mg; 34.6%); finally the unreacted intermediate compound could be recovered.

^{13}C NMR ($CDCl_3$, 62.975 MHz): δ 171.9 (COO); 162.6 (C4); 156.7 (C2); 156.3 (CONH-Val); 155.5 (C2); 152.4 (CONH-4); 146.3 (C6); 136.0 (Ph-C1-Val); 134.9 (Ph-C1-cyt); 128.4-128.0 (2 Ph); 95.1 (C5); 88.9 (C1'); 83.3 (C4'); 77.1 (C3'); 75.0 (C2'); 67.8 (Ph CH_2-Val); 67.0 (Ph CH_2-cyt); 64.7 (C5'); 59.5 (Val-αC); 31.5 (Val-βC); 19.0/18.8 and 17.9/17.7 (Val 2 CH_3).

c) N-(benzyloxycarbonyl)-5'-(N-benzyloxycarbonyl-L-valyl)-3'-stearoyl-araC. A mixture of the intermediate of step b) (97.5mg; 0.16mmol), stearoyl chloride (isomer-free; 97mg; 0.32mmol), triethylamine (50 mg; 0.40 mmol), 4-dimethylaminopyridine (10 mg; 0.08 mmol), and N,N-dimethylformamide (3 ml) was stirred at room temperature for 2h and evaporated in vacuum to small volume. The residue was suspended in a small volume of ethyl acetate and added (with much undissolved amine salts) to a Pasteur pipette 'column' (1 cm. of silica gel; ethyl acetate as eluent). The fractions containing partially purified product were evaporated to dryness and the residue was dissolved in 5 ml of a 50:50 mixture of ethyl acetate - hexane, washed with an aqueous solution of potassium carbonate, and run through another 1 cm. silica gel 'column'. The aqueous phase with salts was extracted with 2 x 1 ml portions of ethyl acetate - hexane which were also eluted

through the 'column'. The combined fractions were evaporated to dryness, yielding 118 mg of a colourless oil which was further purified on a small silica column (ethyl acetate - hexane, 1+1) to give 66.5 mg (47.4%) of pure title compound.

^{13}C NMR ($CDCl_3$, 62.975 MHz): δ 172.5 (stear-COO); 171.8 (Val-COO); 162.6 (C4); 156.0 (CONH-Val); 154.2 (C2); 152.2 (CONH-4); 145.2 (C6); 136.0 (Ph-C1-Val); 134.9 (Ph-C1-cyt); 128.4-127.9 (2 Ph); 94.4 (C5); 88.5 (C1'); 81.3 (C4'); 77.4 (C3'); 73.8 (C2'); 67.9 (Ph CH_2-Val); 67.0 (Ph CH_2-cyt); 63.0 (C5'); 59.1 (Val-αC); 33.8 (stear-C2); 31.7 (stear-C16); 31.0 (Val-βC); 29.5-29.2 (stear-C4-15); 24.5 (stear-C3); 22.5 (stear-C17); 19.0 and 17.5 (Val 2 CH_3); 13.9 (stear-C18).

d) 3'-Stearoyl-5'-L-valyl-araC.

The intermediate of step c) (67 mg; 0.076 mmol) in 4 ml EtOH and 0.4 ml acetic acid with 20 mg of Pd/C 10% was hydrogenated for 0.5h at room temperature and atmospheric pressure to yield, after filtration through Celite, evaporation in vacuum, and freeze-drying with dioxan, 50 mg (99%) of the title compound as a white powder.

^{13}C NMR (DMSO-d_6, 62.975 MHz): δ 171.7 (stear-COO); 170.7 (Val-COO); 165.5 (C4); 156.5 (CONH-Val); 155.5 (C2); 141.8 (C6); 92.4 (C5); 87.0 (C1'); 80.5 (C4'); 78.8 (C3'); 72.6 (C2'); 63.0 (C5'); 57.8 (Val-αC); 33.5 (stear-C2); 31.3 (stear-C16); 29.8 (Val-βC); 29.0-28.4 (stear-C4-15); 24.1 (stear-C3); 22.0 (stear-C17); 18.8 and 18.0 (Val 2 CH_3); 13.7 (stear-C18).

PREPARATIVE EXAMPLE 1

2-(stearoyloxymethyl)-2-(N-(fluorenylmethoxycarbonyl)-L-valyloxymethyl)-propionic acid

To a solution of 2,2-bis(hydroxymethyl) propionic acid (28.16 g, 210 mmole) in water (50 ml), was added potassium hydroxide (11.78 g, 210 mmole). After 5 min,

thc solution was evaporated in vacuo and the residue was coevaporated with dry DMF for three times. The residue was then dissolved in DMF (500 ml), and to the solution was added benzyl bromide (3.57 ml, 30 ml). After stirring for 30 min, the reaction mixture was filtered through the Celite, poured into sodium hydrogen carbonate aqueous solution and extracted with dichloromethane. The organic phase was collected and then washed with sodium hydrogen carbonated aqueous solution. It was then evaporated in vacuo to give benzyl 2,2-bis(hydroxymethyl) propionate (4.37 g).

^{1}H-NMR ($CDCl_3$): 7.35 (s, 5H), 5.20 (d, 2H), 3.91-3.71 (m, 4H), 1.10 (s, 3H).

To a solution of benzyl 2,2-bis(hydroxymethyl) propionate (4.37 g, 19.5 mmole) in pyridine (58 ml) was added dropwise stearoyl chloride (4.13 g, 13.6 mmole) in dichloromethane over 40 min. The reaction was then kept for 16 hr and then poured into sodium hydrogen carbonate aqueous solution and extracted with dichloromethane. The organic phase was collected and evaporated in vacuo. The product benzyl-2-(hydroxymethyl)-2- (stearoyloxymethyl) propionate was isolated by silica gel column chromatography (1.97 g)

^{1}H-NMR ($CDCl_3$): 7.34 (s, 5H), 5.17 (d, 2H), 4.28 (dd, 2H) 3.69 (dd, 2H), 2.24 (t, 2H), 1.57 (m, 2H, 1.25 (s, 28H, 1.22 (s, 3H), 0.87 (t, 3H).

Benzyl 2-(hydroxymethyl)-2-(stearoyloxymethyl) propionate (1.86 g, 3.8 mmole) was dissolved in pyridine (30 ml). To the solution were added toluenesulfonic acid (73 mg, 0.39 mmole), N-fluorenylmethoxycarbonyl-L-valine (3.94 g, 11.6 mmole), and DCC (3.58 g, 17.4 mmole). The reaction was kept at 4 °C for 16 hr and then filtered through Celite. The filtrate was poured into sodium hydrogen carbonate aqueous solution and extracted with dichloromethane. The organic phase was collected and evaporated in vacuo. The product, benzyl-2-(N-fluorenyl-methoxycarbonyl)-L-valyloxymethyl)-2-(stearoyloxymethyl)propionate, was isolated by silica gel column chromatography. Yield: 2.38 g.

^{1}H-NMR ($CDCl_3$): 7.78-7.25 (m, 13H), 5.29 (m, 1H), 5.15 (d, 2H), 4.38 - 4.23 (m, 7H), 2.19 (t, 2H), 2.10 (m, 1H), 1.55 (m, 2H), 1.24 (m, 31H), 0.94 - 0.83 (m, 9H).

To the solution of benzyl 2-(N-(fluorenylmethoxycarbonyl)-L-valyloxymethyl)-2-(stearoyloxymethyl) propionate (1.86 g, 3.8 mmole) in a mixed solvent of THF/methanol (16ml/8ml) were added ammonium formate (376 mg, 6 mmole), formic acid (1.87 ml), and palladium black (40 mg). The reaction was kept at room temperature for 16 hr, and then filtered through Celite. After evaporation, the product was isolated by silica gel column chromatography. Yield: 1.05 g.

PREPARATIVE EXAMPLE 2

1-O-stearoyl-2-O-(N-CBz-L-valyl)glycerol

a) Preparation of 1-O-stearoylglycerol

To a mixture of glycerol (30 g, 326 mmol) and pyridine (25 ml) dissolved in DMF (300 ml) was added dropwise stearoyl chloride (10 g, 33 mmol) dissolved in DMF 100 ml9. The mixture was cooled on an ice bath until addition was complete, whereupon the reaction was maintained under an N_2 atmosphere overnight. After 15 hours CH_2CL_2 (300 ml) and saturated NaHCO3 (aq) was added. The phases were separated and the organic phase washed with water (50 ml) and dried with $Na_2 SO_4$. The solvent and any pyridine were evaporated under vacuum. The crude product was chromatographed on a silica column (CH_2Cl_2 -MeOH, 20:1) and recrystallised (CH_2Cl_2 - ether) to yield around 7 grams.

b) Preparation of pixyl chloride

Acetyl chloride (150 ml, 2.1 mol) is added to a magnetically stirred suspension of 9-hydroxy-9-phenylxanthene (20 g 72 mmol) in benzene (100 ml). An homogenous deep red solution is obtained. The solution is stirred for 30 min. at 20 °C. The volatiles are removed under reduced pressure. Excess AcCl is neutralised by careful addition to ethanol. The residue is coevaporated with toluene (2 x 30 ml) and with

cyclohexane (2 x 30 ml) to obtain a crystalline residue which is stored airtight.Pixyl chloride is alternatively available from Aldrich.

c) Preparation of 1-O-stearoyl, 3-O-pixylglycerol

The product from a) above (2.28 g) and pyridine (25 ml) were mixed and heated until dissolved. After cooling in an icebath pixyl chloride (1.92 g) from step b) was added. The mixture was maintained under agitation and an argon atmoshere in an icebath for half an hour and then at room temperature for 1.5 h. The pyridine was evaporated under vacuum, the residue dissolved in CH_2Cl_2 (70 ml) and washed with 0.5 M citricacid to remove remaining pyridine. The residue was dried with Na_2SO_4, evaporated and chromatographed (ether- hexane 1:3) to give 1.25 g pure product with a TLC R_f around 0.2.

d) Preparation of 1-O-stearoyl, 2-O-(N-CBz-L-valyl), 3-O-pixylglycerol

The product of step c) (237 mg, 0.39 mmol), CBz-L-valine (116 mg, 0.46 mmol), DCC (96 mg, 0.46 mmol) and DMAP (4.7 mg, 0.04 mmol) were dissolved in CH_2Cl_2 (4 ml). The mixture was maintained under agitation in a nitrogen atmosphere overnight. After 18 hours the mixture was filtered through a glass filter and chromatographed on a silica gel column (ether - hexane 1:4) to yield 230 mg with a TLC R_f of 0.2

e) Preparation of 1-O-stearoyl-2-O-(N-CBz-L-valyl)glycerol

The pixyl group in the product of step d) was removed by selective deprotection by the method described in Example 3, step d to yield the title compound.

^{1}H-NMR (CDCl3): δ 7.35 (m, 5H), 5.3-4.9 (m, 4H), 4.35-4.25 (m, 3H), 3.8-3.6 (m, 2H), 2.31-2.25 (m, 2H), 2.20-2.10 (m, 1H), 1.60 (m, 2H), 1.02-0.86 (m, 9H).

PREPARATIVE EXAMPLE 3

1-O-(N-CBz-L-valyl)-2-O-stearoylglycerol

a) Preparation of 1-O-(N-CBz-L-valyl)glycerol.

CBz-L-valine (4.35 g, 17.3 mmol) was added to a fivefold excess of glycerol (8 ml, 86.9 mmol) together with dicyclohexylcarbodiimide (4.29 g 20.8 mmol) and 4-dimethylaminopyridine (0.212 g) at room temperature. After stirring overnight the suspension was filtered and DMF removed in vacuo from the filtrate. The residue was redissolved in CH_2Cl_2, washed successively with saturated $NaHCO_3$, brine, and water and then dried. The crude material was chromatographed on silica gel with 4/1 EtOAc - hexane as eluent to yield 2.465 g. R_f (4/1 EtOAc - hexane) 0.17, (20/1 CH_2Cl_2 - methanol) 0.12.

b) Preparation of 1-O-(N-CBz-L-valyl)-3-O-pixylglyerol

The product of step a) (0.672 g, 20.1 mmol) was dissolved in dry pyridine (3.5 ml) under nitrogen. 9-Chloro-9-phenylxanthene (pixyl chloride, 0.65 g, 22.0 mmol, 1.1 eq - prepared as above) was added and the mixture stirred at room temperature for 1.5 h. MeOH (1.5 ml) was added and the mixture partitioned between 10 ml Et_2O and 10 ml saturated $NaHCO_3$. The aqueous layer was extracted with more ether. The organic layers were combined, dried and concentrated several times with toluene to give a white solid. The crude material was chromatographed on silica gel with 3/1 hexane - EtOAc as eluent to give 0.681 g.

Alternatively a pixyl group can be put on by the procedure described by Gaffney et al, Tetrahedron Lett 1997, 38, 2539-2542 using PxOH and acetic acid.

c) Preparation of 1-O-(N-CBz-L-valyl)-2-O-stearoyl-3-O-pixyl glycerol

Stearoyl chloride (496 ml, 1.3 eq) in 1.5 ml CH_2Cl_2 was added dropwise to a solution of the product of step b) (0.658 g, 1.13 mmol) in 11 ml pyridine with stirring under N_2 in an ice bath. After 15 minus the mixture was stirred at room temperature overnight. The mixture was diluted with 20 ml Et_2O and washed with 10 ml saturated $NaHCO_3$. The aquesous layer was extracted with more Et_2O. The

organic layers were combined, washed with brine (20 ml), dried over Na_2SO_4 and concentrated several times with toluene. The crude material (1.37 g) was chromatographed on 130 g silica gel with 6/1 hexane - EtOAc. An initial fraction of 500 ml was taken followed by 100 ml fractions. The desired material eluted in fractions 2 - 5 yielding 0.748 g.

d) Preparation of 1-O-(N-CBz-L-valyl)-2-O-stearoylglycerol

To a solution of the product of step c) (0.748 g, .872 mmol) dissolved in 35 ml CH_2Cl_2 to make 0.025 M) was added pyrrole (16.5 mol eq) and dichloroacetic acid (5.5 mol eq) at room temperature. TLC after 5 minutes showed complete reaction. The mixture was diluted with 300 ml CH_2Cl_2 and washed with 30 ml saturated $NaHCO_3$. The aqueous layer was extracted with more CH_2Cl_2. The organic phases were combined, washed with brine (30 ml), dried over Na_2SO_4 and concentrated. Crude material was chromatographed on silica gel with 2/1 hexane - EtOAc (with 0.3% acetic acid) as eluent to yield 0.363 g with R_f (2/1 hexane - EtOAc) 0.21.

^{1}H NMR ($CDCl_3$) δ ppm 0.86-0.99 (m, 9H), 1.25 (s, 28H), 1.61 (m, 2H), 2.16 (m, 1H), 2.32 (m, 2H), 3.74 (br s, 2H), 4.28-4.44 (m, 3H), 5.09 (m, 1H), 5.11 (s, 2H), 5.22 (d, 1H), 7.36 (m, 5H)

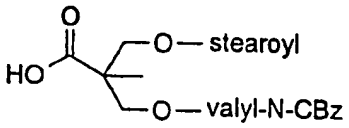
PREPARATIVE EXAMPLE 4

1-O-stearoyl-3-O-(NCBz-L-valyl)glycerol

The product of Preparative Example 2, part a) (2.86 g, 7.99 mmol), DCC (0.9g, 4.36 mmol) 4-(N,N-dimethyl)aminopyridine (DMAP) (0.048 mg, 0.39 mmol) and N-CBz-L-valine (1g, 3.98 mmol) were dissolved in CH_2Cl_2 (60 ml) and DMF (6 ml). The reaction was left at ambient temperature for 18 hours and then filtrated. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 ml) and filtrated. The crude title compound was purified by chromatography [SiO2, ether/hexane (1:2)] to yield 1.3 g of the desired product. Unreacted 1-stearoylglycerol may be recovered by eluting with CH_2Cl_2/MeOH (20:1).

^{1}H-NMR ($CDCl_3$): δ 5.25 (d, 1H), 5.11 (s, 2H), 4.30-4.05 (m, 6H), 2.65 (d, 1H), 2.35 (t, 2H), 2.06 (m, 1H), 1.62 (m, 2H), 1.26 (s, 28H), 1.00-0.84 (m, 9H).

PREPARATIVE EXAMPLE 5



A solution of stearoyl chloride (12.1g, 40 mmol, 1.0 eq) in CH_2Cl_2 (100 ml) was slowly (1h) added to a solution of 2,2-bis(hydroxymethyl)propionic acid (26.8 g, 200 mmol, 5.0 eq) in pyridine (400 ml) at room temperature. The reaction mixture was stirred at room temperature overnight and thereafter concentrated (100 ml) under vacuum. The reaction mixture was slowly treated with saturated $NaHCO_3$ (400 ml) and thereafter extracted with CH_2Cl_2 (3x300 ml). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The crude material was chromatographed on Silica gel (500 g) with 19/1 to 4/1 CH_2Cl_2-MeOH as eluent, to yield the monostearoyl ester with R_f (9/1 CH_2Cl_2-MeOH) of 0.33. 12.5 g (78 %).

A solution of N-Cbz-L-valine (18.85 g, 75 mmol, 2.4 eq) and DMAP (855 mg, 7 mmol, 0.22 eq) in CH_2Cl_2 (800 ml) was cooled to 0° C and treated with DCC (14.4 g, 70 mmol, 2.2 eq). The reaction mixture was stirred at room temperature for 30 min and thereafter slowly (1h) treated with a solution of the above monostearoyl ester (12.5 g, 31.2 mmol, 1 eq) in $CHCl_3$ (200 ml, free of ethanol). After stirring overnight the suspention was filtered and the filtrate was washed with brine, dried with Na_2SO_4 and concentrated in vacuum. The crude material was chromatographed on silica gel (500 g) with 19/1 to 4/1 CH_2Cl_2-MeOH as eluent, to yield the above depicted di-ester with R_f (9/1 CH_2Cl_2-MeOH) of 0.46. 13.8 g (70 %)

^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.35-7.3 (m, 5H, ArH), 5.32 (d, 1H, CH), 5.10 (s, 2H, CH_2Ph), 4.33-4.18 (m, 4H, CH_2), 2.28 (t, 2H, CH_2), 2.22-2.05 (m, 1H, CH), 1.65-1.50 (m, 2H, CH_2) 1.35-1.15 (m, 31H), 1.00-0.82 (m, 9H, Me).

PREPARATIVE EXAMPLE 6

5-(N-trityl-L-valyloxymethyl)-6-stearoyloxyhexanoic acid

a) Preparation of 2-allyl 1,3-propanediol

Diethyl allylmalonate (20 ml, 101 mmol) in anhydrous ether (100 ml) was added dropwise to a stirred solution of lithium aluminium hydride (9.6 g, 253 mmol) at 0°C. The reaction was warmed up to room temperature and kept for 5 hours. It was cooled down to 0 °C and water (12 ml) was carefully added dropwise. After stirring for 30 min, the mixture was filtered through Celite and then washed with ethanol (2 x 500 ml). The solution was dried under vacuum giving 9.5 g product

^{1}H-NMR ($CDCl_3$): 5.78 m, 1H), 5.03 (m, 2H), 3.78 (m, 2H), 3.69 (m, 2H), 2.06 (t, 2H), 1.87 (m, 1H).

b) Preparation of 1-O-(N-trityl-L-valyl)-2-allyl-1,3-propandiol

To a solution of N-trityl-L-valine (5.5 g, 15.2 mmole), 2-allyl-1,3-propandiol (4.4 g, 38 mmol), N,N-dimethylamino pyridine (183 mg, 1.5 mmol) in dichloromethane (120 ml) was added DCC (3.5 g, 16.7 mmol). The reaction was kept under reflux overnight. After filtration through Celite, the organic phase was washed with sodium hydrogen carbonate aqueous solution and dried . Silica gel column chromatography gave 4.6 g intermediate 1-O-(N-trityl-L-valyl)-2-allyl-1,3-propandiol.

c) Preparation of 1-O-(N-trityl-L-valyl)-2-allyl-3-stearoyl-1,3-propandiol.

To a solution of 1-O-(N-trityl-L-valyl)-2-allyl-1,3-propandiol (1.83 g, 4 mmol) in dichloromethane (40 ml) and pyridine (3.2 ml, 40 mmol) at 0 °C was added dropwise stearoyl chloride (3.62 g, 12 mmol) in dichloromethane. The solution was warmed up to room temperature, and kept for 3 hr. It was then washed with sodium

hydrogen carbonate aqueous solution and dried. The product was isolated by silica gel column chromatography. 1.9 g

^{1}H-NMR ($CDCl_3$): 7.30 (m, 15 H), 5.70 (m, 1H), 4.99 (m, 2H), 3.93 (m, 2H), 3.55 (m, 1H), 3.27 (m, 2H), 2.68 (m, 1H), 2.30 (m, 2H), 2.23 (m, 1H), 2.01 (m, 2H), 1.85 (m, 1H), 1.62 (m, 2H), 1.3 (m, 28H), 0.98 (dd, 6H), 0.91 (t, 3H).

d) Preparation of 3-(N-trityl-L-valyloxymethyl)-4-stearoyloxy-butyraldehyde
1-O-(N-trityl-L-valyl)-2-allyl-3-stearoyl-1,3-propandiol (580 mg, 0.8 mmol) was dissolved in dioxanc (5 ml). To the solution were added osmium tetraoxide (20 mg, 0.08 mmole) and pyridine (0.05 ml, 0.64 mmole). A solution of sodium periodate in water (3.5 ml) was added to the reaction mixture. The reaction was kept overnight and then cooled down to 0 °C. An aqueous solution of sodium hydrogen sulfite was added and the mixture was extracted with dichloromethane. The organic phase was dried and purified by silica gel column chromatography. Yield. 250 mg

^{1}H-NMR ($CDCl_3$): 9.68 (s, 1H), 7.25 (m, 15 H), 3.92 (m, 2H), 3.58 (m, 1H), 2.32 (m, 2H), 2.68 (m, 1H), 2.34 (m, 7 H), 1.58 (m, 2H), 1.53 (m, 28 H), 0.96 (dd, 6H), 0.86 (t, 3H).

f) Preparation of benzyl 3-(N-trityl-L-valyloxymethyl)-4-stearoyloxyhexen-2-oate
To the solution of 3-(N-trityl-L-valyloxymethyl)-4-stearoyloxy-butyraldehyde (15.8 g, 21.8 mmole) were added (benzyloxycarbonylmethyl) triphenylphosphonium bromide (10.7 g, 21.8 mmole) and triethylamine (2.21 g, 21.8 mmole). The reaction was kept overnight at room temperature, and the mixture was evaporated. To the residue was added diethyl ether (200 ml and kept at 4 °C for two hours. It was then filtered and the filtrate was evaporated and the product was purified by silica gel column chromatography. Yield. 10 g

^{1}H-NMR ($CDCl_3$): 7.30 (m, 20 H), 6.89 (m, 1H), 5.88 (d, 1H), 5.19 (d, 2H), 3.95 (m, 2H), 3.57 (m, 1H), 3.29 (, 2H), 2.68 (m, 1H), 2.23 (m, 5H), 1.93 (m, 1H), 1.60 (m, 2H), 1.32 (m, 28 H), 0.95 (dd, 6H), 0.89 (t, 3 H).

g) Preparation of 3-(N-trityl-L-valyloxymethyl)-4-stearoyloxyhexanoic acid
To a solution of benzyl 3-(N-trityl-L-valyloxymethyl)-4-stearoyloxyhexen-2-oate (70 mg, 0.08 mmole) in methanaol (3 ml) and ethyl acetate (1 ml) was added sodium hydrogen carbonate (10 mg) and palladium black (20 mg). The reaction was kept under hydrogen at atmospheric pressure for 2 hr. The mixture was filtered and evaporated. The residue was dissolved in dichloromethane and washed successively with aqueous EDTA solution and cold aqueous 2 % citric solution. The organic phase was evaporated to give 61 mg product

^{1}H-NMR ($CDCl_3$): 7.30 (m, 15 H), 3.93 (m, 2H), 3.57 (m, 1H), 3.25 (m, 2H), 2.30 (dt, 4H), 2.20 (m, 1H), 1.70 (m, 1H), 1.62 (m, 4H), 1.30 (m, 28 H), 0.95 (dd, 6 H), 0.87 (t, 3 H).

PREPARATIVE EXAMPLE 7

3-(N-benzyloxycarbonyl-L-valyloxymethyl)-4-stearoyloxy-butyric acid

a) Preparation of 1-O-(N-benzyloxycarbonyl-L-valyl)-2-allylyl-1,3-propandiol
To a solution of 2-allyl-1,3-propandiol (4.6 g, 40 mmole) and N-benzyloxycarbonyl valine (5.02 g, 20 mmole) in dichloromethane was added dimethylaminopyridine (244 mg, 2 mmol), and DCC (4.5 g, 22 mmol). After two hours, the mixture was filtered through Celite, evaporated and the product, 1-O-(N-benzyloxycarbonyl-L-valyl)-2- allylyl-1,3-propandiol, isolated to yield 5.01 g.

^{1}H-NMR ($CDCl_3$): 7.36 (m, 5H), 5.78 (m, 1H), 5.26 (d, 1H), 5.11 (s, 2H), 5.06 (d, 2H), 4.22 (m, 3H), 3.59 (m, 2H), 2.13 (m, 3H), 1.98 (m, 2H), 0.94 (dd, 6 H).

b) Preparation of 1-O-(N-benzyloxycarbonyl-L-valyl)-2-allylyl-3-O-stearoyl-1,3-propandiol
To a solution of 1-O-(N-benzyloxycarbonyl-L-valyl)-2-allylyl-1,3-propandiol (4.46 g, 12.7 mmol) in dichloromethane (70 ml) and pyridine (6.1 ml, 76 mmole) in ice bath was added stearoyl chloride (7.8 g, 26 mmole). The reaction mixture was

warmed up to room temperature and kept for one hour. It was then poured into aqueous sodium hydrogen carbonate solution, the organic phase was dried and the product 1-O-(N-benzyloxycarbonyl-L-valyl)-2-allylyl-3-O-stearoyl-1,3-propandiol was purified by silica gel column chromatography. 6.7 g

1H-NMR ($CDCl_3$): 7.34 (m, 5H), 5.77 (m, 1H), 5.30 (d, 1H), 5.11 (s , 2H), 5.08 (d, 2H), 4.32 (m, 1H), 4.10 (m, 4 H), 2.29 (t, 2H), 2.13 (m, 4H), 1.62 (m, 3 H), 1.25 (m, 28H), 0.90 (m, 9 H).

c) Preparation of 3-(N-benzyloxycarbonyl-L-valyloxymethyl)-4-stearoyloxy-butyric acid.

Potassium permanganate (756 mg, 4.8 mmole) was dissolved in water (7.5 ml). The solution was kept under strong stirring for 10 min. A solution of 1-O-(N-benzyloxycarbonyl-L-valyl)-2-allylyl-3-O-stearoyl-1,3-propandiol (1 g, 1.6 mmol) and tetrabutylammonium bromide (77 mg, 0.24 mmole) in benzene (5 ml) was added. The slurry was stirred for 1.5 hr, and dichloromethane was added. A sodium bisulfite aqueous solution was added to the slurry until the mixture discolored. The organic phase was acidified with acetic acid and washed with water. After evaporation, the product 3 -(N-benzyloxycarbonyl-L-valyloxymethyl)-4-stearoyloxy-butyric acid (390 mg) was isolated by silica gel column chromatography.

^{1}H-NMR ($CDCl_3$): 7.33 (m, 5H), 5.38 (d, 1H), 5.11 (s, 2H), 4.14 (m, 5 H); 2.60 (m, 1H), 2.45 (m, 2 H), 2.29 (t, 2 H), 2.18 (m, 1 H), 1.58 (m, 2 H), 1.25 (m, 28 H), 0.90 (m, 9 H).

PREPARATIVE EXAMPLE 8

3-[1-(N-CBz-L-valyl)-2-stearoyl] propyl chloroformate

1-(N-CBz-L-valyl)-2-stearoyl) glycerol (300 mg, 0.5 mmole) was dissolved in 20 % phosgene in toluene (15 ml). After 18 h, the solution was evaporated and the residue was coevaporated with toluene for several time, giving title product in

quantitative yield. This product forms a carbonate with the target nucleoside using standard methodology, for instance reacting in a 10:1 DMF/pyridine solution at 0°C for 3 to 24 hours, pouring into $NaHCO_3$ solution and extraction with dichloromethane. The amino acid is deprotected, for instance with palladium black in a methanol, ethyl acetate, acetic acid solution to yield the nucleoside-O-[1-(L-valyl)-2-stearoyl-3-propyloxy carbonyl]

^{1}H-NMR ($CDCl_3$): 7.40 (m, 5H), 5.28 (m, 2H), 5.10 (s, 2H), 4.35 (m, 5H), 2.35 (m, 2H), 2.17 (m, 1 H), 1.56 (m, 2H), 1.30 (m, 28 H), 0.95 (m, 9H).

PREPARATIVE EXAMPLE 9

5-(N-FMOC-L-valyloxy)-4-stearoyloxy-pentanoic acid

a) Benzyl 4,5-dihydroxy-2-pentenoate.

A mixture of DL-glyceralaldehyde (4,5g , 50 mmole) and (benzyloxycarbonylmethyl)-triphenyl-phosphoniumbromide (24.57g, 50 mmole) in 100 ml 1,2-epoxybutane was refluxed overnight . The mixture was evaporated under vacuum and the product was isolated by silica gel chromatography .
Yield : 8g = 71 %

^{1}H - NMR ($CDCl_3$) 2.50 (s, 1H) 2.96 (s, 1H) 3.54 (m, 1H) 3.70 (m, 1H) 4.38 (m, 1H) 5.12 (s, 2H) 6.14 (m,1H) 6.90 (m, 1H) 7.30 (m, 5H)

b) Benzyl 5-(N-FMOC-L-valyloxy)-4-hydroxy-2-pentenoate.

A mixture of benzyl 4,5-dihydroxy-2-pentenoate (4.4g, 20 mmole), N-FMOC-L-valine (5.8g, 17 mmole) and DMAP (0.21g, 1,7 mmole) in 100 ml dichloromethane was cooled to about 10°C . A solution of DCC (4.2g, 20 mmole) in 25 ml dichloromethane was added droppwise at the same temperature and the mixture was stirred overnight at room temperature. The mixture was cooled to 5°C and the urethane was filtered . The filtrate was evaporated under reduced pressure and the product was isolated by silica gel column chromatography .
Yield : 6,6g = 71%

^{1}H-NMR ($CDCl_3$) 0.91 (m, 6H) 2.12 (m, 1H) 4.38 (m, 5H) 5.14 (s, 2H) 5.24 (m, 1H) 6.20 (m, 1H) 6.92 (m, 1H) 7.30 (m, 13H)

c) Benzyl-5-(N-FMOC-L-valyloxy)-4-stearoyloxy-2-pentenoate

To a solution of benzyl-5-(N-FMOC-L-valyloxy)-4-hydroxy-2-pentenoate (6.5g, 12 mmol) and pyridine (2.0g, 25 mmole) in 100 ml dichloromethane at 10°C was added dropwise a solution of stearoylchloride (4.55g , 15 mmol) in 25 ml dichloromethane. The mixture was stirred overnight.100 ml of 5% sodium hydrogencarbonate solution was added and the mixture was stirred for 30 minutes . The organic phase was seperated and the water phase was extracted two times with dichloromethane.The combined organic phases were dried with sodium sulfate and concentrated in vacuo. The product was isolated by silica gel column chromatography .Yield : 7,8g = 80%

^{1}H-NMR ($CDCl_3$) 0.88 (m, 9H) 1.25 (m, 28H) 1.58 (m, 2H) 2.14 (m, 1H) 2.32 (m, 2H) 4.22 (m, 5H) 5.19 (s, 2H) 5.25 (m, 1H) 6.12 (m, 1H) 6.85 (m, 1H) 7.35 (m, 13H).

d) 5-(N-FMOC-L-valyloxy)-4-stearoyloxy-pentanoic acid.

A solution of benzyl 5-(N-FMOC-L-valyloxy)-4-stearoyloxy-2-pentenoate (3.8g, 4.69 mmole) in 50 ml ethyl acetate was hydrogenated with 10% palladium on charcoal (0,5g) at normal pressure for five hours at room temperature. The catalyst was filtered and washed with ethyl acetate and 1,4-dioxane. The solution was evaporated under reduced pressure .Yield : 3.3g = 99%

^{1}H-NMR ($CDCl_3$) 0.92 (m, 9H) 1.25 (m, 28H) 1.54 (m, 2H) 1.98 (m, 2H) 2.18 (m, 1H) 2.28 (m, 2H) 2.41 (m, 2H) 4,32 (m, 5H) 5.13 (m, 1H) 5.33 (m,1H) 7.50 (m, 8H)

PREPARATIVE EXAMPLE 10

3-(N-FMOC-L-valyloxy)-2-stearoyloxypropionic acid

a) Benzyl 2,3-dihydroxypropionate .

A mixture of D,L-glyceric acid, calcium salt dihydrate (2.9g, 10 mmole) and benzylbromide (3.8g, 22 mmole) in 25 ml DMF was stirred at 60°C overnight . The mixture was evaporated under reduced pressure and the product was isolated by silica gel chromatography. Yield : 4g = 100%

^{1}H-NMR ($CDCl_3$) 3.26 (s, 1H) 3.90 (m, 2H) 4.32 (m, 1H) 5.25 (s, 2H) 7.28 (m, 5H)

b) Benzyl 3-(N-FMOC-L-valyloxy)-2-hydroxypropionate

A solution of benzyl-2,3-dihydroxypropionate (4,0g , 20 mmole) N-FMOC-L-valine (5.4g, 16 mmole) and DMAP(0.2g, 1.6 mmole) in 80 ml dichloromethane was cooled to about 10°C . A solution of DCC (4.12g, 20 mmole) in 25 ml was added dropwise at the same temperature and the mixture was stirred overnight at room temperature. The mixture was cooled to 5°C and the urethane was filtered .

The solution was evaporated under reduced pressure and the product was isolated by silica gel chromatography. Yield : 4.7g = 45%

^{1}H-NMR ($CDCl_3$) 0.88 (m, 6H) 2.05 (m,1H) 4.40 (m, 6H) 5.23 (m, 3H) 7.50 (m, 13H)

c) Benzyl 3-(N-FMOC-L-valyloxy)-2-stearoyloxypropionate

To a stirred solution of benzyl 3-(N-FMOC-L-valyloxy)-2-hydroxypropionate (4.6g 8.89 mmole) and pyridine (1.41g, 17.8 mmole) in 80 ml dichloromethane was added dropwise a solution of stearoylchloride (3.64g, 12 mmole) in 20 ml dichloromethane and the mixture was stirred overnight at room temperature. 100 ml of 5% sodium hydrogencarbonate solution was added and the mixture stirred for

30 minutes. The organic phase was seperated and the water phase was extracted two times with dichloromethane. The combined organic phases were dried with sodium sulfate and concentrated in vacuo. The product was isolated by silica gel chromatography. Yield : 6.1g = 87%

^{1}H-NMR ($CDCl_3$) 0.88 (m, 9H) 1.26 (m, 28H) 1.56 (m, 2H) 2.06 (m, 1H) 2.34 (m, 2H) 4.36 (m, 6H) 5.19 (s, 2H) 5.32 (m, 1H) 7.50 (m, 13H)

d) 3- (N-FMOC-L-valyloxy)-2-stearoyloxypropionic acid.

A solution of benzyl 3-(N-FMOC-L-valyloxy)-2-stearoyloxypropionate (0.78g, 1 mmole) in 20 ml ethyl acetate was hydrogenated with 10% palladium on charcoal (0.2g) at normal pressure for three hours at room temperature . The catalyst was filtered and washed with ethyl acetate and 1,4-dioxane. The solution was evaporated under reduced pressure. Yield : 0.63g = 90%

^{1}H-NMR ($CDCl_3$) 0.88 (m, 9H) 1.24 (m, 28H) 1.40 (m, 2H) 2.12 (m, 3H) 4.30 (m, 5H) 5.16 (m,1H) 5.60 (m,1H) 7.40 (m, 8H)

PREPARATIVE EXAMPLE 11

1-(N-Benzyloxycarbonyl-L-valyloxymethyl)-2-stearoyloxyethoxycarbonyl chloride

Bis(trichloromethyl) carbonate (160 mg; 0.54 mmol) was added with stirring to a solution of 1-(N-benzyloxycarbonyl-L-valyl)-3-stearoylglycerol; 1-(N-benzyloxycarbonyl-L-valyloxy)-3-stearoyloxy-2-propanol; preparative example 4; (660 mg; 1.12 mmol) and triethylamine (200 mg; 2.0 mmol) in dichloromethane (5 ml) at room temperature. After 1h, n-hexane (10 ml) was added and the precipitated triethylamine hydrochloride was filtered off through a short column of silica gel, the product eluted with a further amount of n-hexane, and the solvent evaporated in vacuum to yield 650 mg (89%) of the title compound.

^{13}C NMR ($CDCl_3$, 62.975 MHz): δ 172.8 (stear-COO); 171.2 (Val-COO); 155.9 (CONH); 154.1 (COCl); 136.0 (Ph-C1-Val); 128.1-127.7 (Ph); 67.2 (CHOH); 66.7 (Ph CH_2); 63.1 (ValCOOCH_2); 61.8 (stear-COOCH_2); 58.7 (Val-αC); 33.7 (stear-C2); 31.6 (stear-C16); 31.0 (Val-βC); 29.3-28.8 (stear-C4-15); 24.5 (stear-C3); 18.6 and 17.1 (Val 2 CH_3); 13.8 (stear-C18).

PREPARATIVE EXAMPLE 12

3- (N-CBz-L-valyloxymethyl)-4-stearoyloxybutylchloroformate

a) 3- (N-CBz-L-valyoxymethyl)-4-stearoyloxy-butanol .

To a stirred solution of 4-stearoyloxy-3-(N-CBz-L-valyloxymethylbutyraldehyde (prepared analogously to preparative example 6, step d) using CBz protected valine) (2.0 g, 3.2 mmole) in 25 ml methanol at 10°C was added sodium borohydride (0.6g, 16 mmole) in small portions . The mixture was stirred for 30 minutes and then acidified with acetic acid .The mixture was diluted with water and extracted three times with dichloromethanc.The organic phase was dried with sodium sulfatc and concentrated in vacuo .The product was isolated by silica gel column chromatography. Yield: 1,5g = 75%.

^1H-NMR ($CDCl_3$) 0.88 (m, 9H) 1.25 (m, 28H) 1.52 (m, 4H) 2.24 (m, 3H) 3.68 (m, 2H) 4.12 (m, 4H) 4.24 (m, 1H) 5.08 (s , 2H) 5.22 (m, 1H) 7.36 (m, 5H)

b) 3-(N-CBz-L-valyloxymethyl)-4-stearoyloxybutyl chloroformate

A solution of the intermediate of step a) in 20 ml of a 20% solution of phosgene in toluene was stirred overnight . The mixture was evaporated under reduced pressure to yield the title compound.Yield 1.5g = 97%.

^1H-NMR ($CDCl_3$) 0.88 (m, 9H) 1.28 (m, 28H) 1.58 (m, 2H) 1.72 (m, 2H) 2.15 (m, 1H) 2.31 (m, 2H) 4.08 - 4.42 (m, 5H) 5.10 (s, 2H) 5.22 (m, 1H) 7.36 (m, 5H)

EXAMPLE 9

5'-O-(5-Valyloxymethyl-6-stearoyloxy)hexanoyl ribavirin

A mixture of 5'-O-(5-N-trityl-valyloxymethyl-6-stearoyloxy)hexanoic acid (0.97 g; 1.26 mmol), DCC (0.303 g; 1.47 mmol), ribavirin (0.256 g; 1.05 mmol) and DMAP (14 mg; 0.11 mmol) in DMF (10 mL) was stirred for 24 h at room temperature. After evaporation the residue was purified by chromatography on silica gel by eluting with CH_2Cl_2, 2.5 % MeOH in CH_2Cl_2 and 5 % MeOH in CH_2Cl_2. The product was deprotected with acetic acid (10 mL) at room temperature, evaporated and purified by chromatography on silica gel by eluting with CH_2Cl_2, 5 % MeOH in CH_2Cl_2 and 20 % MeOH in CH_2Cl_2 to give 72 mg of the title product as the acetate salt.

^{1}H NMR (250 MHz, MeOD-d_4) δ 8.70 (s, 1H), 5.84 (d, 1H), 4.19-4.02 (m, 6H), 3.78-3.55 (m, 2H), 3.40 (br s, 1H), 2.37 (t, 2H), 2.25 (t, 2H), 2.00 (m, 2H), 1.87-1.32 (m, 6H), 1.20 (s, 28H), 0.96-0.73 (m, 9H).

EXAMPLE 10

4'O-[2-Stearoyloxy-1-(L-valyloxymethyl)ethoxycarbonyl]ganciclovir

a) 4'O-[1-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-stearoyloxyethoxycarbonyl]ganciclovir.

A mixture of 1-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-stearoyloxyethoxycarbonyl chloride (654 mg; 1.0 mmol), ganciclovir (220 mg; 0.86 mmol), triethylamine (200 mg; 2.0 mmol), and 4-dimethylaminopyridine (30 mg; 0.25 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 24h. Undissolved salts were filtered off and the solution was evaporated in vacuum to small volume. The residue was purified by chromatography on silica gel (8 g). Elution with ethyl acetate + methanol + water (15+2+1) with slight warming of the column to avoid crystallisation yielded 149 mg (20%) of 9-{1-[1-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-

stearoyloxyethoxycarbonyloxymethyl]-2-hydroxyethoxymethyl}guanine after evaporation in vacuum.

^{13}C NMR ($CDCl_3$, 62.975 MHz): δ 173.0 (stear-COO); 171.5 (Val-COO); 158.6 (C6); 156.1 (CONH); 154.5 (OCOO); 154.1 (C2); 151.1 (C4); 137.9 (C8); 136.3 (Ph-C1-Val); 128.4-127.8 (Ph); 116.5 (C5); 78.7 ($\underline{C}HOCH_2$); 73.2 ($\underline{C}HOCO$); 72.4 (OCH_2N); 67.3 ($ValCOO\underline{C}H_2$); 67.0 ($PhCH_2$); 66.0 ($stear\text{-}COO\underline{C}H_2$); 62.5 ($OCOO\underline{C}H_2$); 61.5 ($CH_2OH$); 58.7 (Val-αC); 33.7 (stear-C2); 31.6 (stear-C16); 31.0 (Val-βC); 29.3-28.8 (stear-C4-15); 24.5 (stear-C3); 22.5 (stear-C17); 18.6 and 17.1 (Val 2 CH_3); 13.8 (stear-C18).

b) 4'O-[2-Stearoyloxy-1-(L-valyloxymethyl)ethoxycarbonyl]ganciclovir.
The product of step a) (149 mg; 0.17 mmol) in 5 ml EtOH and 0.5 ml acetic acid with 100 mg of Pd/C 10% was hydrogenated overnight at room temperature and atmospheric pressure to yield, after filtration through Celite and evaporation in vacuum, 110.5 mg (81%) as a solid, the title product 9-{1-[2-stearoyloxy-1-(L-valyloxymethyl)ethoxycarbonyloxymethyl]-2-hydroxyethoxymethyl}guanine as the acetate.

^{13}C NMR ($CDCl_3$, 62.975 MHz): δ 173.0 (stear-COO); 171.5 (Val-COO); 158.6 (C6); 154.5 (OCOO); 154.1 (C2); 151.1 (C4); 137.9 (C8); 115.5 (C5); 78.5 ($\underline{C}HOCH_2$); 73.4 ($\underline{C}HOCO$); 72.5 (OCH_2N); 67.5 ($ValCOO\underline{C}H_2$); 66.1 ($stear\text{-}COO\underline{C}H_2$); 62.2 ($OCOO\underline{C}H_2$); 61.6 ($CH_2OH$); 59.0 (Val-αC); 33.7 (stear-C2); 31.7 (stear-C16); 30.7 (Val-βC); 29.3-28.8 (stear-C4-15); 24.6 (stear-C3); 22.5 (stear-C17); 19.0-17.2 (Val 2 CH_3); 13.9 (stear-C18).

EXAMPLE 11

9-{1-[4-Stearoyloxy-3-(L-valyloxymethyl)butyryloxymethyl]-2-hydroxyethoxymethyl}guanine

a) 9-{1-[3-(N-Benzyloxycarbonyl-L-valyloxymethyl)-4-stearoyloxybutyryloxymethyl]-2-hydroxyethoxymethyl}guanine.

3-(N-benzyloxycarbonyl-L-valyloxymethyl)-4-stearoyloxybutyric acid; preparative example 7 (634 mg; 1.00 mmol) was dissolved in dichloromethane (5 ml), thionyl chloride (400 mg; 3.36 mmol) and 4 drops of N,N-dimethylformamide were added, and the mixture was kept at room temperature for 2h, then carefully evaporated to small volume in vacuum to yield crude acid chloride. Ganciclovir sodium salt (280 mg; 1.00 mmol) was suspended in N,N-dimethylformamide (5 ml), and triethylamine (100 mg; 1.0 mmol), 4-dimethylaminopyridine (20 mg; 0.16 mmol), and the crude acid chloride in a small amount of N,N-dimethylformamide were added. The mixture was stirred efficiently for 2 days at room temperature. After filtration through a small amount of silica gel, the filtrate was evaporated in vacuum to small volume. Chromatography on silica gel, then on alumina, using ethyl acetate + methanol + water (15+2+1) as eluent, yielded 168 mg (19%) of 4'O-[3-(N-benzyloxycarbonyl-L-valyloxymethyl)-4-stearoyloxybutyryl]ganciclovir

^{1}H NMR ($CDCl_3$): δ 12.0 (br s, 1H, 1-NH); 7.8 (s, 1H, 8-H); 7.3 (br, 5H, Ph); 6.7 (br s, 2H, 2-NH_2); 5.6 (d, 1H, OCONH); 5.5 (s, 2H, OCH_2N); 5.1 (br, 2H, $PhCH_2$); 4.3 (d, 1H, Val-αC); 4.2-4.0 (m, 7H, 3x$COOCH_2$, CHO); 3.7 (m, 2H, CH_2OH); 2.5 (m, 1H, $CHCH_2COO$); 2.4 (d, 2H, $CHCH_2COO$); 2.3 (t, 2H, stear-2-CH_2); 2.15 (m, 1H, Val βC); 1.55 (quint, 2H, stear-3-CH_2); 1.3-1.2 (m, 28H, stear-CH_2); 1.0-0.8 (dd, 6H, Val CH_3); 0.85 (t, 3H, stear-18-CH_3).

^{13}C NMR ($CDCl_3$, 62.975 MHz): δ 173.6 (stear-COO); 172.0 ($CHCH_2COO$); 171.4 (Val-COO); 158.4 (C6); 156.3 (CONH); 154.0 (C2); 151.6 (C4); 138.9 (C8); 136.0 (Ph-C1); 128.4-127.9 (Ph); 116.8 (C5); 77.6 ($CHOCH_2$); 72.5 (OCH_2N); 67.0 ($PhCH_2$); 64.1 ($ValCOOCH_2$); 63.0 (stear-$COOCH_2$); 62.0 ($COOCH_2CH$); 61.6 (CH_2OH); 59.0 (Val-αC); 34.1 ($CHCH_2COO$); 33.9 (stear-C2); 32.7 ($CHCH_2COO$); 31.8 (stear-C16); 30.9 (Val-βC); 29.6 -28.9 (stear-C4-15); 24.7 (stear-C3); 22.5 (stear-C17); 18.9 and 17.4 (Val 2 CH_3); 14.0 (stear-C18).

b) 9-{1-[4-Stearoyloxy-3-(L-valyloxymethyl)butyryloxymethyl]-2-hydroxyethoxymethyl}guanine.

The title compound was synthesized from 4'O-[3-(N-benzyloxycarbonyl-L-valyloxymethyl)-4-stearoyloxybutyryl]ganciclovir(100 mg), using the same procedure as for Example 10 b) above, yielding 80 mg of 4'O-[4-Stearoyloxy-3-(L-valyloxymethyl)butyryl]ganciclovir (87%) as the acetate salt, a white crystalline product.

^{13}C NMR ($CDCl_3$, 62.975 MHz): δ 173.5 (stear-COO); 171.7 ($CHCH_2\underline{C}OO$); 171.2 (Val-COO); 158.4 (C6); 156.3 (CONH); 154.0 (C2); 151.5 (C4); 138.2 (C8); 115.5 (C5); 79.0 (OCH_2N); 64.4 ($ValCOO\underline{C}H_2$); 63.2 ($stear\text{-}COO\underline{C}H_2$); 61.7 ($COO\underline{C}H_2CH$ and CH_2OH); 58.7 (Val-αC); 34.2 ($\underline{C}HCH_2COO$); 34.0 (stear-C2); 32.6 ($CH\underline{C}H_2COO$); 31.8 (stear-C16); 30.9 (Val-βC); 29.6-28.9 (stear-C4-15); 24.7 (stear-C3); 22.6 (stear-C17); 18.9 and 17.5 (Val 2 CH_3); 14.0 (stear-C18).

EXAMPLE 12

9-{5-O- [3-(L-valyloxymethyl)-4-stearoyloxybutanoyl]arabinofuranosyl}guanine

a) 9-{5-O-[3-(N-CBz-L-valyloxymethyl)-4-stearoyloxybutanoyl]arabino-furanosyl}guanine.

To a solution of 9-arabinofuranosyl guanine (110 mg, 0.42 mmole) and 3-(N-CBz-L-valyloxymethyl)-4-stearoyloxybutyric acid (355 mg, 0.55 mmole) in DMF (15 ml) were added dimethylaminopyridine (7 mg), 1-hydroxybenzotriazole (73 mg, 0.55 mmole) and DCC (135 mg, 0.65 mmole). After two days, the reaction mixture was filtered and the filtrate was poured into sodium hydrogen carbonate solution and extracted with dichloromethane. The organic phase was dried and the product 9-{5-O-[3-(N-CBz-L-valyloxymethyl)-4-stearoyloxybutanoyl]arabino-furanosyl}guanine was isolated with a silica gel column. 41 mg.

^{1}H-NMR (DMSO-δ6):7.70 (s, 1H), 7.42 (m, 5 H), 6.48 (s, 2H), 5.40 (d, 1H), 4.30 - 3.0 (m, 9 H), 2.45 (m, 3 H), 2.37 (t, 2 H), 2.05 (m, 1 H), 1.47 (m, 2 H), 1.22 (m, 28 H), 0.85 (m, 9 H).

To a solution of 9-{5-O- [3-(N-CBz-L-Valyloxymethyl)-4-stearoyloxy-butanoyl-]-arabinofuranosyl-}-guanine in a mixed solvent of methanol (3 ml), ethyl acetate (1 ml) and acetic acid (0.5 ml) was added palladium black (30 mg). After reaction under hydrogen atomasphere for 18 h, the reaction mixture was filtered and the filtrate was dried. The titled product was isolated by silica gel column. 18 mg.

^{1}H-NMR (DMSO-d6): 7.57 (s, 1H), 6.59 (s, 2H), 6.05 (d, 1 H), 4.40 - 3.90 (m, 9 H), 2.45 (m, 3H), 2.26 (t, 2H), 1.70 (m, 1H), 1.47 (m, 2 H), 1.22 (m, 28 H), 0.82 (m, 9H).

FORMULATION EXAMPLE1

Tablet formulation

The following ingredients are screened through a 0.15 mm sieve and dry-mixed

10 g	9-(4-Stearoyloxy-3-(L-valyloxymethyl)butyl) guanine
40 g	lactose
49 g	crystalline cellulose
1 g	magnesium stearate

A tabletting machine is used to compress the mixture to tablets containing 250 mg of active ingredient.

FORMULATION EXAMPLE 2

Enteric coated tablet

The tablets of Formulation Example 1 are spray coated in a tablet coater with a solution comprising

120 g	ethyl cellulose
30 g	propylene glycol
10g	sorbitan monooleate
ad	1 000 ml aq. dist.

FORMULATION EXAMPLE 3

Controlled release formulation

50 g 9-(4-Stearoyloxy-3-(L-isoleucyloxymethyl)butyl) guanine:
12 g hydroxypropylmethylcellulose (Methocell K15)
4.5 g lactose

are dry-mixed and granulated with an aqueous paste of povidone. Magnesium stearate (0.5 g) is added and the mixture compressed in a tabletting machine to 13 mm diameter tablets containing 500 mg active agent.

FORMULATION EXAMPLE 4

Soft capsules

250 g 9-((1-Stearoyloxy-3-(L-isoleucyloxy)-2-propoxy)-methyl) guanine:
100 g lecithin
100 g arachis oil

The compound of the invention is dispersed in the lecithin and arachis oil and filled into soft gelatin capsules.

BIOLOGICAL EXAMPLE 1

Bioavailability testing

The bioavailability of representative compounds of the invention were compared to the respective parent compound in a rat model. Compounds of the invention and comparative compounds were administered, per oral, to multiples of three individually weighed animals to give 0.1 mmol/kg of the dissolved prodrug in a propylene glycol vehicle. Comparative example 1 (penciclovir) and Comparative example 2 (ganciclovir) was from the same batch as used for preparation of the relevant Examples. The animals were fasted from 5 hours before to approximately 17 hours after administration and were maintained in metabolic cages. Urine was

collected for the 24 hours following administration and frozen until analysis. Parent compound was analysed in the urine using the HPLC/UV assay of Ståhle & Öberg, Antimicrob Agents Chemother. 36 No 2, 339-342 (1992), modified as follows: samples upon thawing are diluted 1:100 in aq dist H_2O and filtered through an amicon filter with centrifugation at 3000 rpm for 10 minutes. Duplicate 30 µl samples are chromatographed on an HPLC column; Zorbax SB-C18; 75 x 4.6 mm; 3.5 micron; Mobile phase 0.05M NH_4PO_4, 3 - 4 % methanol, pH 3.3 - 3.5; 0.5 ml/min; 254 nm, retention time for PCV/GCV at MeOH 4% and pH 3.33, ~12.5 min. Bioavailability is calculated as the measured parent compound recovery from each animal averaged over at least three animals and expressed as a percentage of the averaged 24 hour urinary parent compound recovery from a group of 4 individually weighed rats respectively injected i.v.jugularis with 0.1 mmol/kg parent compound in a Ringer's buffer vehicle and analysed as above. Results are presented in Table 1.

TABLE 1

Compound	R_1	R_2	Bioavailability
Comparative example 1	hydrogen	hydrogen	1.5 %
Example 4	valyl	stearoyl	22.7 %
Example 6	isoleucyl	valyl	26.3 %
Comparative example 2	hydrogen	hydrogen	10.6 %
Comparative example 3	valyl	valyl	29.6%
Example 1	valyl	stearoyl	47.8 %

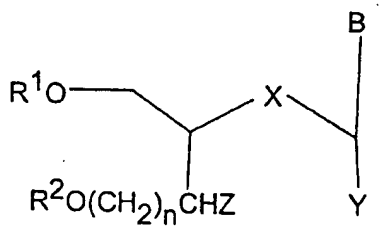
Comparison of the bioavailabilities of the compounds of the invention with the comparative example indicates that the particular combination of the fatty acids and amino acids produce bioavailabilities significantly greater than the respective mother compound and in this assay system signifiantly greater than the prior art divalyl prodrug.

It will be appreciated that although various aspects of the invention have been illustrated with stearoyl and valyl as the respective fatty and amino acid esters, the homologous nature of the fatty acids and aliphatic amino acids as defined in the claims is such that comparable methodology and performance can be expected from the respective claimed variables. Similarly, it will be apparent that the invention can be applied to a multitude of nucleoside analogues as that expression is understood in the pharmaceutic art, both cyclic and acyclic.

CLAIMS

1. A nucleoside analogue comprising at least two hydroxy functions on the sugar or acyclic moieties, one of which sugar or acyclic hydroxy functions is esterified with an aliphatic amino acid and the other of which is esterified with a saturated or monounsaturated, optionally substituted fatty acid having 6 to 22 carbon atoms, with the proviso that the nucleoside analogue is not 9-[4-hydroxy-(2-hydroxymethyl)butyl]guanine or its 6-deoxy derivative; or wherein the aliphatic amino acid and fatty esters are esterified to a common linker group, which linker group is bonded to one of said hydroxy functions.

2. A nucleoside analogue according to claim 1 with the formula I



where B is a natural or unnatural nucleotide base,

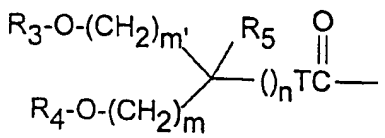
X is O or CH_2

Y and Z are each H, or together form a bond, or Y is methylene or -CH(OH)-and Z is a bond thereto;

n is 0 or 1; and

one of R_1 and R_2 is the acyl residue of the aliphatic amino acid and the other is the acyl residue of the fatty acid; or

one of R_1 and R_2 is hydrogen or an acyl residue of an aliphatic amino acid or fatty acid as defined; and the other is a structure of the formula II:



II

where one of R_3 and R_4 is the acyl residue of the aliphatic amino acid and the other is the acyl residue of the fatty acid;

R_5 is H or C_1-C_3 alkyl;

T is a bond, -O- or -NH-;

m and m' are independently 0, 1 or 2 and n is 0-5.

3. A compound according to claim 1 wherein the aliphatic amino acid ester is L-valyl or L-isoleucyl.

4. A compound according to claim 1 wherein the fatty acid ester has 12 to 22 carbon atoms, including the carbonyl.

5. A compound according to claim 4 wherein the fatty acid is stearoyl, cicasanoyl or behenoyl, or n9-octadecenoyl, n9-eicosenoyl or n11-docosenoyl.

6. A compound according to claim 2 wherein B is guanine or guanine modified in the 6 position.

7. A compound according to claim 2 wherein B is cytosine, substituted benzimidazol-3-yl or 1,2,4-triazole-3-carboxamide.

8. A compound according to claim 2 wherein X is O or CH_2 and Y and Z are H.

9. A compound according to claim 2 wherein formula I defines an arabinose, ribose, 2-deoxyribose or 2',3'-hydroxymethylcyclobutyl moiety.

10. A compound according to claim 2 wherein T is -O- or a bond, m' is 1 and n is 0-2.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10 in conjunction with a pharmaceutically acceptable carrier or diluent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01903

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07H 19/06, C07H 19/067, C07H 19/16, C07H 19/167, C07D 473/18, C07D 473/32, C07D 473/34, A61K 31/52, A61K 31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07H, C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9730051 A1 (MEDIVIR AB), 21 August 1997 (21.08.97) --	1-10
A	WO 9424134 A1 (HOECHST AKTIENGESELLSCHAFT), 27 October 1994 (27.10.94) --	1-10
A	WO 8903837 A1 (PRONEURON, INC.), 5 May 1989 (05.05.89) --	1-10
A	EP 0375329 A2 (THE WELLCOME FOUNDATION LIMITED), 27 June 1990 (27.06.90) --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" erlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 1998	24.02.1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01903

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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P,A	WO 9727197 A1 (F. HOFFMANN-LA ROCHE AG), 31 July 1997 (31.07.97) --	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/98

International application No.
PCT/SE 97/01903

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